

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C12N 15/51, C12Q 1/68 C12N 15/40, C12Q 1/70 A61K 39/29, C07K 13/00 G01N 33/576	A2	(11) International Publication Number: WO 92/19743 (43) International Publication Date: 12 November 1992 (12.11.92)
(21) International Application Number: PCT/US92/04036 (22) International Filing Date: 8 May 1992 (08.05.92) (30) Priority data: 697,326 8 May 1991 (08.05.91) US (71) Applicant: CHIRON CORPORATION [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US). (72) Inventors: CHA, Tai-An ; 964 Springview Circle, San Ramon, CA 94583 (US). BEALL, Eileen ; 1150 Lincoln Avenue, # 5, Walnut Creek, CA 94596 (US). IRVINE, Bruce ; 3401 El Monte Drive, Concord, CA 94519 (US). KOLBERG, Janice ; 131 Scots Valley, Hercules, CA 94547 (US). URDEA, Michael, S. ; 100 Bunce Meadow Road, Alamo, CA 94501 (US).		(74) Agent: JANIUK, Anthony, J.; Wolf, Greenfield & Sacks, 600 Atlantic Avenue, Boston, MA 02210 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: HCV GENOMIC SEQUENCES FOR DIAGNOSTICS AND THERAPEUTICS (57) Abstract The present application features nucleic acid, peptide and antibody compositions relating to genotypes of hepatitis C virus and methods of using such compositions for diagnostic and therapeutic purposes.		

Am

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
DE	Germany	MC	Monaco	TG	Togo
DK	Denmark			US	United States of America

HCV GENOMIC SEQUENCES FOR
DIAGNOSTICS AND THERAPEUTICS

This application is a continuation-in-part of U.S.
5 Serial No. 07/697,326 entitled "Polynucleotide Probes
Useful for Screening for Hepatitis C Virus, filed May
8, 1991.

Technical Field

10 The invention relates to compositions and methods
for the detection and treatment of hepatitis C virus,
(HCV) infection, formerly referred to as blood-borne
non-A, non-B hepatitis virus (NANBV) infection. More
specifically, embodiments of the present invention
15 feature compositions and methods for the detection of
HCV, and for the development of vaccines for the
prophylactic treatment of infections of HCV, and
development of antibody products for conveying passive
immunity to HCV.

20

Background of the Invention

The prototype isolate of HCV was characterized in
U.S. Patent Application Serial No. 122,714 (See also
EPO Publication No. 318,216). As used herein, the term
25 "HCV" includes new isolates of the same viral species.
The term "HCV-1" referred to in U.S. Patent Application
Serial No. 122,714.

- 2 -

HCV is a transmissible disease distinguishable from other forms of viral-associated liver diseases, including that caused by the known hepatitis viruses, i.e., hepatitis A virus (HAV), hepatitis B virus (HBV), and delta hepatitis virus (HDV), as well as the hepatitis induced by cytomegalovirus (CMV) or Epstein-Barr virus (EBV). HCV was first identified in individuals who had received blood transfusions.

The demand for sensitive, specific methods for screening and identifying carriers of HCV and HCV contaminated blood or blood products is significant. Post-transfusion hepatitis (PTH) occurs in approximately 10% of transfused patients, and HCV accounts for up to 90% of these cases. The disease frequently progresses to chronic liver damage (25-55%).

Patient care as well as the prevention of transmission of HCV by blood and blood products or by close personal contact require reliable screening, diagnostic and prognostic tools to detect nucleic acids, antigens and antibodies related to HCV.

Information in this application suggests the HCV has several genotypes. That is, the genetic information of the HCV virus may not be totally identical for all HCV, but encompasses groups with differing genetic information.

Genetic information is stored in thread-like molecules of DNA and RNA. DNA consists of covalently

SUBSTITUTE SHEET

- 3 -

linked chains of deoxyribonucleotides and RNA consists of covalently linked chains of ribonucleotides. Each nucleotide is characterized by one of four bases: adenine (A), guanine (G), thymine (T), and cytosine (C). The bases are complementary in the sense that, due to the orientation of functional groups, certain base pairs attract and bond to each other through hydrogen bonding and π -stacking interactions. Adenine in one strand of DNA pairs with thymine in an opposing complementary strand. Guanine in one strand of DNA pairs with cytosine in an opposing complementary strand. In RNA, the thymine base is replaced by uracil (U) which pairs with adenine in an opposing complementary strand. The genetic code of living organism is carried in the sequence of base pairs. Living cells interpret, transcribe and translate the information of nucleic acid to make proteins and peptides.

The HCV genome is comprised of a single positive strand of RNA. The HCV genome possesses a continuous, translational open reading frame (ORF) that encodes a polyprotein of about 3,000 amino acids. In the ORF, the structural protein(s) appear to be encoded in approximately the first quarter of the N-terminus region, with the majority of the polyprotein responsible for non-structural proteins.

SUBSTITUTE SHEET

- 4 -

The HCV polyprotein comprises, from the amino terminus to the carboxy terminus, the nucleocapsid protein (C), the envelope protein (E), and the non-structural proteins (NS) 1, 2 (b), 3, 4 (b), and 5.

5 HCV of differing genotypes may encode for proteins which present an altered response to host immune systems. HCV of differing genotypes may be difficult to detect by immuno diagnostic techniques and nucleic acid probe techniques which are not specifically
10 directed to such genotype.

Definitions for selected terms used in the application are set forth below to facilitate an understanding of the invention. The term "corresponding" means homologous to or complementary to
15 a particular sequence of nucleic acid. As between nucleic acids and peptides, corresponding refers to amino acids of a peptide in an order derived from the sequence of a nucleic acid or its complement.

The term "non-naturally occurring nucleic acid" refers to a portion of genomic nucleic acid, cDNA, semisynthetic nucleic acid, or synthetic origin nucleic acid which, by virtue of its origin or manipulation:
(1) is not associated with all of a nucleic acid with which it is associated in nature, (2) is linked to a
25 nucleic acid or other chemical agent other than that to

- 5 -

which it is linked in nature, or (3) does not occur in nature.

Similarly the term, "a non-naturally occurring peptide" refers to a portion of a large naturally occurring peptide or protein, or semi-synthetic or synthetic peptide, which by virtue of its origin or manipulation (1) is not associated with all of a peptide with which it is associated in nature, (2) is linked to peptides, functional groups or chemical agents other than that to which it is linked in nature, or (3) does not occur in nature.

The term "primer" refers to a nucleic acid which is capable of initiating the synthesis of a larger nucleic acid when placed under appropriate conditions. The primer will be completely or substantially complementary to a region of the nucleic acid to be copied. Thus, under conditions conducive to hybridization, the primer will anneal to a complementary region of a larger nucleic acid. Upon addition of suitable reactants, the primer is extended by the polymerizing agent to form a copy of the larger nucleic acid.

The term "binding pair" refers to any pair of molecules which exhibit mutual affinity or binding capacity. For the purposes of the present application, the term "ligand" will refer to one molecule of the binding pair, and the term "antiligand" or "receptor"

SUBSTITUTE SHEET

- 6 -

or "target" will refer to the opposite molecule of the binding pair. For example, with respect to nucleic acids, a binding pair may comprise two complementary nucleic acids. One of the nucleic acids may be
5 designated the ligand and the other strand is designated the antiligand receptor or target. The designation of ligand or antiligand is a matter of arbitrary convenience. Other binding pairs comprise, by way of example, antigens and antibodies, drugs and
10 drug receptor sites and enzymes and enzyme substrates, to name a few.

The term "label" refers to a molecular moiety capable of detection including, by way of example, without limitation, radioactive isotopes, enzymes,
15 luminescent agents, precipitating agents, and dyes.

The term "support" includes conventional supports such as filters and membranes as well as retrievable supports which can be substantially dispersed within a medium and removed or separated from the medium by
20 immobilization, filtering, partitioning, or the like. The term "support means" refers to supports capable of being associated to nucleic acids, peptides or antibodies by binding partners, or covalent or noncovalent linkages.

25 A number of HCV strains and isolates have been identified. When compared with the sequence of the original isolate derived from the USA ("HCV-1"; see

SUBSTITUTE SHEET

- 7 -

Q.-L. Choo et al. (1989) Science 244:359-362, Q.-L. Choo et al. (1990) Brit. Med. Bull. 46:423-441, Q.-L. Choo et al., Proc. Natl. Acad. Sci. 88:2451-2455 (1991), and E.P.O. Patent Publication No. 318,216, cited supra, it was found that a Japanese isolate ("HCV J1") differed significantly in both nucleotide and polypeptide sequence within the NS3 and NS4 regions. This conclusion was later extended to the NS5 and envelope (E1/S and E2/NS1) regions (see K. Takeuchi et al., J. Gen. Virol. (1990) 71:3027-3033, Y. Kubo, Nucl. Acids. Res. (1989) 17:10367-10372, and K. Takeuchi et al., Gene (1990) 91:287-291). The former group of isolates, originally identified in the United States, is termed "Genotype I" throughout the present disclosure, while the latter group of isolates, initially identified in Japan, is termed "Genotype II" herein.

Brief Description of the Invention

The present invention features compositions of matter comprising nucleic acids and peptides corresponding to the HCV viral genome which define different genotypes. The present invention also features methods of using the compositions corresponding to sequences of the HCV viral genome which define different genotypes described herein.

SUBSTITUTE SHEET

- 8 -

A. Nucleic acid compositions

The nucleic acid of the present invention, corresponding to the HCV viral genome which define different genotypes, have utility as probes in nucleic acid hybridization assays, as primers for reactions involving the synthesis of nucleic acid, as binding partners for separating HCV viral nucleic acid from other constituents which may be present, and as anti-sense nucleic acid for preventing the transcription or translation of viral nucleic acid.

One embodiment of the present invention features a composition comprising a non-naturally occurring nucleic acid having a nucleic acid sequence of at least eight nucleotides corresponding to a non-HCV-1 nucleotide sequence of the hepatitis C viral genome. Preferably, the nucleotide sequence is selected from a sequence present in at least one region consisting of the NS5 region, envelope 1 region, 5'UT region, and the core region.

Preferably, with respect to sequences which correspond to the NS5 region, the sequence is selected from a sequence within a sequence numbered 2-22. The sequence numbered 1 corresponds to HCV-1. Sequences numbered 1-22 are defined in the Sequence Listing of the application.

Preferably, with respect to sequences corresponding to the envelope 1 region, the sequence is

- 9 -

selected from a sequence within sequences numbered 24-32. Sequence No. 23 corresponds to HCV-1. Sequences numbered 23-32 are set forth in the Sequence Listing of the application.

5 Preferably, with respect to the sequences which correspond to the 5'UT regions, the sequence is selected from a sequence within sequences numbered 34-51. Sequence No. 33 corresponds to HCV-1. Sequence No. 33-51 are set forth in the Sequence Listing of this
10 application.

 Preferably, with respect to the sequences which correspond to the core region, the sequence is selected from a sequence within the sequences numbered 53-66. Sequence No. 52 corresponds to HCV-1. Sequences 52-66
15 are set forth in the Sequence Listing of this application.

 The compositions of the present invention form hybridization products with nucleic acid corresponding to different genotypes of HCV.

20 HCV has at least five genotypes, which will be referred to in this application by the designations GI-GV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences
25 numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV,

SUBSTITUTE SHEET

- 10 -

is exemplified by sequences numbered 20-22, and 29-31 and 48-49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

One embodiment of the present invention features
5 compositions comprising a nucleic acid having a sequence corresponding to one or more sequences which exemplify a genotype of HCV.

B. Method of forming a Hybridization Product

10 Embodiments of the present invention also feature a method of forming a hybridization product with nucleic acid having a sequence corresponding to HCV nucleic acid. One method comprises the steps of placing a non-naturally occurring nucleic acid having a
15 non-HCV-1 sequence corresponding to HCV nucleic acid under conditions in which hybridization may occur. The non-naturally occurring nucleic acid is capable of forming a hybridization product with HCV nucleic acid, under hybridization conditions. The method further
20 comprises the step of imposing hybridization conditions to form a hybridization product in the presence of nucleic acid corresponding to a region of the HCV genome.

The formation of a hybridization product has
25 utility for detecting the presence of one or more genotypes of HCV. Preferably, the non-naturally occurring nucleic acid forms a hybridization product

- 11 -

with nucleic acid of HCV in one or more regions comprising the NS5 region, envelope 1 region, 5'UT region and the core region. To detect the hybridization product, it is useful to associate the non-naturally occurring nucleic acid with a label. The formation of the hybridization product is detected by separating the hybridization product from labeled non-naturally occurring nucleic acid, which has not formed a hybridization product.

The formation of a hybridization product has utility as a means of separating one or more genotypes of HCV nucleic acid from other constituents potentially present. For such applications, it is useful to associate the non-naturally occurring nucleic acid with a support for separating the resultant hybridization product from the the other constituents.

Nucleic acid "sandwich assays" employ one nucleic acid associated with a label and a second nucleic acid associated with a support. An embodiment of the present invention features a sandwich assay comprising two nucleic acids, both have sequences which correspond to HCV nucleic acids; however, at least one non-naturally occurring nucleic acid has a sequence corresponding to non-HCV-1 HCV nucleic acid. At least one nucleic acid is capable of associating with a label, and the other is capable of associating with a support. The support associated non-naturally

SUBSTITUTE SHEET

- 12 -

occurring nucleic acid is used to separate the hybridization products which include an HCV nucleic acid and the non-naturally occurring nucleic acid having a non-HCV-1 sequence.

5 One embodiment of the present invention features a method of detecting one or more genotypes of HCV. The method comprises the steps of placing a non-naturally occurring nucleic acid under conditions which hybridization may occur. The non-naturally occurring
10 nucleic acid is capable of forming a hybridization product with nucleic acid from one or more genotypes of HCV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences
15 numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified sequences numbered 20-22 and 29-31. The fifth genotype, GV, is exemplified by sequences
20 numbered 18, 19, 50 and 51.

 The hybridization product of HCV nucleic acid with a non-naturally occurring nucleic acid having non-HCV-1 sequence corresponding to sequences within the HCV genome has utility for priming a reaction for the
25 synthesis of nucleic acid.

 The hybridization product of HCV nucleic acid with a non-naturally occurring nucleic acid having a

- 13 -

sequence corresponding to a particular genotype of HCV has utility for priming a reaction for the synthesis of nucleic acid of such genotype. In one embodiment, the synthesized nucleic acid is indicative of the presence
5 of one or more genotypes of HCV.

The synthesis of nucleic acid may also facilitate cloning of the nucleic acid into expression vectors which synthesize viral proteins.

Embodiments of the present methods have utility as
10 anti-sense agents for preventing the transcription or translation of viral nucleic acid. The formation of a hybridization product of a non-naturally occurring nucleic acid having sequences which correspond to a particular genotype of HCV genomic sequencing with HCV
15 nucleic acid may block translation or transcription of such genotype. Therapeutic agents can be engineered to include all five genotypes for inclusivity.

C. Peptide and antibody composition

A further embodiment of the present invention
20 features a composition of matter comprising a non-naturally occurring peptide of three or more amino acids corresponding to a nucleic acid having a non-HCV-1 sequence. Preferably, the non-HCV-1 sequence corresponds with a sequence within one or more regions
25 consisting of the NS5 region, the envelope 1 region, the 5'UT region, and the core region.

SUBSTITUTE SHEET

- 14 -

Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence of the NS5 region, the sequence is within sequences numbered 2-22. The sequence numbered 1 corresponds to HCV-1. Sequences numbered 1-22 are set forth in the Sequence Listing.

Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence of the envelope 1 region, the sequence is within sequences numbered 24-32. The sequence numbered 23 corresponds to HCV-1. Sequences numbered 23-32 are set forth in the Sequence Listing.

Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence directed to the core region, the sequence is within sequences numbered 53-66. Sequence numbered 52 corresponds to HCV-1. Sequences numbered 52-66 are set forth in the Sequence Listing.

The further embodiment of the present invention features peptide compositions corresponding to nucleic acid sequences of a genotype of HCV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified

SUBSTITUTE SHEET

- 15 -

sequences numbered 20-22, 29-31, 48 and 49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

5 The non-naturally occurring peptides of the present invention are useful as a component of a vaccine. The sequence information of the present invention permits the design of vaccines which are inclusive for all or some of the different genotypes of HCV. Directing a vaccine to a particular genotype
10 allows prophylactic treatment to be tailored to maximize the protection to those agents likely to be encountered. Directing a vaccine to more than one genotype allows the vaccine to be more inclusive.

The peptide compositions are also useful for the
15 development of specific antibodies to the HCV proteins. One embodiment of the present invention features as a composition of matter, an antibody to peptides corresponding to a non-HCV-1 sequence of the HCV genome. Preferably, the non-HCV-1 sequence is
20 selected from the sequence within a region consisting of the NS5 region, the envelope 1 region, and the core region. There are no peptides associated with the untranslated 5'UT region.

Preferably, with respect to antibodies directed to
25 peptides of the NS5 region, the peptide corresponds to a sequence within sequences numbered 2-22. Preferably, with respect to antibodies directed to a peptide

SUBSTITUTE SHEET

- 16 -

corresponding to the envelope 1 region, the peptide corresponds to a sequence within sequences numbered 24-32. Preferably, with respect to the antibodies directed to peptides corresponding to the core region,
5 the peptide corresponds to a sequence within sequences numbered 53-66.

Antibodies directed to peptides which reflect a particular genotype have utility for the detection of such genotypes of HCV and therapeutic agents..

10 One embodiment of the present invention features an antibody directed to a peptide corresponding to nucleic acid having sequences of a particular genotype. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The
15 second genotype, GII, is exemplified by the sequences numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified sequences numbered 20-22, 29-31, 48 and
20 49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

Individuals skilled in the art will readily recognize that the compositions of the present invention can be packaged with instructions for use in
25 the form of a kit for performing nucleic acid hybridizations or immunochemical reactions.

SUBSTITUTE SHEET

- 17 -

The present invention is further described in the following figures which illustrate sequences demonstrating genotypes of HCV. The sequences are designated by numerals 1-145, which numerals and sequences are consistent with the numerals and sequences set forth in the Sequence Listing. Sequences 146 and 147 facilitate the discussion of an assay which numerals and sequences are consistent with the numerals and sequences set forth in the Sequence Listing.

Brief Description of the Figures and Sequence Listing

Figure 1 depicts schematically the genetic organization of HCV;

Figure 2 sets forth nucleic acid sequences numbered 1-22 which sequences are derived from the NS5 region of the HCV viral genome;

Figure 3 sets forth nucleic acid sequences numbered 23-32 which sequences are derived from the envelope 1 region of the HCV viral genome;

Figure 4 sets forth nucleic acid sequences numbered 33-51 which sequences are derived from the 5'UT region of the HCV viral genome; and,

Figure 5 sets forth nucleic acid sequences numbered 52-66 which sequences are derived from the core region of the HCV viral genome.

The Sequence Listing sets forth the sequences of sequences numbered 1-147.

SUBSTITUTE SHEET

- 18 -

Detailed Description of the Invention

The present invention will be described in detail as as nucleic acid having sequences corresponding to the HCV genome and related peptides and binding
5 partners, for diagnostic and therapeutic applications.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, and immunology, which are within the skill of the
10 art. Such techniques are explained fully in the literature. See e.g., Maniatis, Fitsch & Sambrook, Molecular Cloning; A Laboratory Manual (1982); DNA Cloning, Volumes I and II (D.N Glover ed. 1985);
Oligonucleotide Synthesis (M.J. Gait ed, 1984); Nucleic
15 Acid Hybridization (B.D. Hames & S.J. Higgins eds. 1984); the series, Methods in Enzymology (Academic Press, Inc.), particularly Vol. 154 and Vol. 155 (Wu and Grossman, eds.).

The cDNA libraries are derived from nucleic acid
20 sequences present in the plasma of an HCV-infected chimpanzee. The construction of one of these libraries, the "c" library (ATCC No. 40394), is described in PCT Pub. No. WO90/14436. The sequences of the library relevant to the present invention are set
25 forth herein as sequence numbers 1, 23, 33 and 52.

Nucleic acids isolated or synthesized in accordance with features of the present invention are

- 19 -

useful, by way of example without limitation as probes, primers, anti-sense genes and for developing expression systems for the synthesis of peptides corresponding to such sequences.

5 The nucleic acid sequences described define genotypes of HCV with respect to four regions of the viral genome. Figure 1 depicts schematically the organization of HCV. The four regions of particular interest are the NS5 region, the envelope 1 region, the
10 5'UT region and the core region.

 The sequences set forth in the present application as sequences numbered 1-22 suggest at least five genotypes in the NS5 region. Sequences numbered 1-22 are depicted in Figure 2 as well as the Sequence
15 Listing. Each sequence numbered 1-22 is derived from nucleic acid having 340 nucleotides from the NS5 region.

 The five genotypes are defined by groupings of the sequences defined by sequence numbered 1-22. For convenience, in the present application, the different
20 genotypes will be assigned roman numerals and the letter "G".

 The first genotype (GI) is exemplified by sequences within sequences numbered 1-6. A second genotype (GII) is exemplified by sequences within
25 sequences numbered 7-12. A third genotype (GIII) is exemplified by the sequences within sequences numbered 13-17. A fourth genotype (GIV) is exemplified by

SUBSTITUTE SHEET

- 20 -

sequences within sequences numbered 20-22. A fifth genotype (GV) is exemplified by sequences within sequences numbered 18 and 19.

5 The sequences set forth in the present application as sequences numbered 23-32 suggest at least four genotypes in the envelope 1 region of HCV. Sequences numbered 23-32 are depicted in Figure 3 as well as in the Sequence Listing. Each sequence numbered 23-32 is derived from nucleic acid having 100 nucleotides from
10 the envelope 1 region.

A first envelope 1 genotype group (GI) is exemplified by the sequences within the sequences numbered 23-25. A second envelope 1 genotype (GII) region is exemplified by sequences within sequences
15 numbered 26-28. A third envelope 1 genotype (GIII) is exemplified by the sequences within sequences numbered 29-31. A fourth envelope 1 genotype (GIV) is exemplified by the sequences within sequence numbered 32.

The sequences set forth in the present application
20 as sequences numbered 33-51 suggest at least three genotypes in the 5'UT region of HCV. Sequences numbered 33-51 are depicted in Figure 4 as well as in the Sequence Listing. Each sequence numbered 33-51 is derived from the nucleic acid having 252 nucleotides
25 from the 5'UT region, although sequences 50 and 51 are somewhat shorter at approximately 180 nucleotides.

SUBSTITUTE SHEET

- 21 -

The first 5'UT genotype (GI) is exemplified by the sequences within sequences numbered 33-38. A second 5'UT genotype (GII) is exemplified by the sequences within sequences numbered 39-45. A third 5'UT genotype (GIII) is exemplified by the sequences within sequences numbered 46-47. A fourth 5'UT genotype (GIV) is exemplified by sequences within sequences numbered 48 and 49. A fifth 5'UT genotype (GV) is exemplified by sequences within sequences numbered 50 and 51.

10 The sequences numbered 48-62 suggest at least three genotypes in the core region of HCV. The sequences numbered 52-66 are depicted in Figure 5 as well as in the Sequence Listing.

15 The first core region genotype (GI) is exemplified by the sequences within sequences numbered 52-57. The second core region genotype (GII) is exemplified by sequences within sequences numbered 58-64. The third core region genotype (GIII) is exemplified by sequences within sequences numbered 65 and 66. Sequences
20 numbered 52-65 are comprised of 549 nucleotides. Sequence numbered 66 is comprised of 510 nucleotides.

The various genotypes described with respect to each region are consistent. That is, HCV having features of the first genotype with respect to the NS5
25 region will substantially conform to features of the first genotype of the envelope 1 region, the 5'UT region and the core region.

SUBSTITUTE SHEET

- 22 -

Nucleic acid isolated or synthesized in accordance with the sequences set forth in sequence numbers 1-66 are useful as probes, primers, capture ligands and anti-sense agents. As probes, primers, capture ligands and anti-sense agents, the nucleic acid will normally comprise approximately eight or more nucleotides for specificity as well as the ability to form stable hybridization products.

10 Probes

A nucleic acid isolated or synthesized in accordance with a sequence defining a particular genotype of a region of the HCV genome can be used as a probe to detect such genotype or used in combination with other nucleic acid probes to detect substantially all genotypes of HCV.

With the sequence information set forth in the present application, sequences of eight or more nucleotides are identified which provide the desired inclusivity and exclusivity with respect to various genotypes within HCV, and extraneous nucleic acid sequences likely to be encountered during hybridization conditions.

Individuals skilled in the art will readily recognize that the nucleic acid sequences, for use as probes, can be provided with a label to facilitate detection of a hybridization product.

- 23 -

Capture Ligand

For use as a capture ligand, the nucleic acid selected in the manner described above with respect to probes, can be readily associated with supports. The manner in which nucleic acid is associated with supports is well known. Nucleic acid having sequences corresponding to a sequence within sequences numbered 1-66 have utility to separate viral nucleic acid of one genotype from the nucleic acid of HCV of a different genotype. Nucleic acid isolated or synthesized in accordance with sequences within sequences numbered 1-66, used in combinations, have utility to capture substantially all nucleic acid of all HCV genotypes.

15 Primers

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility as primers for the amplification of HCV sequences. With respect to polymerase chain reaction (PCR) techniques, nucleic acid sequences of eight or more nucleotides corresponding to one or more sequences of sequences numbered 1-66 have utility in conjunction with suitable enzymes and reagents to create copies of the viral nucleic acid. A plurality of primers having different sequences corresponding to more than one genotype can be used to create copies of viral nucleic acid for such genotypes.

SUBSTITUTE SHEET

- 24 -

The copies can be used in diagnostic assays to detect HCV virus. The copies can also be incorporated into cloning and expression vectors to generate polypeptides corresponding to the nucleic acid synthesized by PCR, as will be described in greater detail below.

Anti-sense

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility as anti-sense genes to prevent the expression of HCV.

Nucleic acid corresponding to a genotype of HCV is loaded into a suitable carrier such as a liposome for introduction into a cell infected with HCV. A nucleic acid having eight or more nucleotides is capable of binding to viral nucleic acid or viral messenger RNA. Preferably, the anti-sense nucleic acid is comprised of 30 or more nucleotides to provide necessary stability of a hybridization product of viral nucleic acid or viral messenger RNA. Methods for loading anti-sense nucleic acid is known in the art as exemplified by U.S. Patent 4,241,046 issued December 23, 1980 to Papahadjopoulos et al.

Peptide Synthesis

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility to

- 25 -

generate peptides. The sequences exemplified by sequences numbered 1-32 and 52-66 can be cloned into suitable vectors or used to isolate nucleic acid. The isolated nucleic acid is combined with suitable DNA
5 linkers and cloned into a suitable vector. The vector can be used to transform a suitable host organism such as E. coli and the peptide encoded by the sequences isolated.

10 Molecular cloning techniques are described in the text Molecular Cloning: A Laboratory Manual, Maniatis et al., Coldspring Harbor Laboratory (1982).

The isolated peptide has utility as an antigenic substance for the development of vaccines and
15 antibodies directed to the particular genotype of HCV.

Vaccines and Antibodies

The peptide materials of the present invention have utility for the development of antibodies and
vaccines.

20 The availability of cDNA sequences, or nucleotide sequences derived therefrom (including segments and modifications of the sequence), permits the construction of expression vectors encoding antigenically active regions of the peptide encoded in
25 either strand. The antigenically active regions may be derived from the NS5 region, envelope 1 regions, and the core region.

SUBSTITUTE SHEET

- 26 -

Fragments encoding the desired peptides are derived from the cDNA clones using conventional restriction digestion or by synthetic methods, and are ligated into vectors which may, for example, contain portions of fusion sequences such as beta galactosidase or superoxide dismutase (SOD), preferably SOD. Methods and vectors which are useful for the production of polypeptides which contain fusion sequences of SOD are described in European Patent Office Publication number 0196056, published October 1, 1986.

Any desired portion of the HCV cDNA containing an open reading frame, in either sense strand, can be obtained as a recombinant peptide, such as a mature or fusion protein; alternatively, a peptide encoded in the cDNA can be provided by chemical synthesis.

The DNA encoding the desired peptide, whether in fused or mature form, and whether or not containing a signal sequence to permit secretion, may be ligated into expression vectors suitable for any convenient host. Both eukaryotic and prokaryotic host systems are presently used in forming recombinant peptides. The peptide is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use. Purification may be by techniques known in the art, for example, differential extraction, salt fractionation, chromatography on ion exchange resins, affinity chromatography, centrifugation, and

SUBSTITUTE SHEET

- 27 -

the like. See, for example, Methods in Enzymology for a variety of methods for purifying proteins. Such peptides can be used as diagnostics, or those which give rise to neutralizing antibodies may be formulated into vaccines. Antibodies raised against these peptides can also be used as diagnostics, or for passive immunotherapy or for isolating and identifying HCV.

An antigenic region of a peptide is generally relatively small--typically 8 to 10 amino acids or less in length. Fragments of as few as 5 amino acids may characterize an antigenic region. These segments may correspond to NS5 region, envelope 1 region, and the core region of the HCV genome. The 5'UT region is not known to be translated. Accordingly, using the cDNAs of such regions, DNAs encoding short segments of HCV peptides corresponding to such regions can be expressed recombinantly either as fusion proteins, or as isolated peptides. In addition, short amino acid sequences can be conveniently obtained by chemical synthesis. In instances wherein the synthesized peptide is correctly configured so as to provide the correct epitope, but is too small to be immunogenic, the peptide may be linked to a suitable carrier.

A number of techniques for obtaining such linkage are known in the art, including the formation of disulfide linkages using N-succinimidyl-3-(2-

SUBSTITUTE SHEET

- 28 -

- pyridylthio)propionate (SPDP) and succinimidyl 4-(N-maleimido-methyl)cyclohexane-1-carboxylate (SMCC) obtained from Pierce Company, Rockford, Illinois, (if the peptide lacks a sulfhydryl group, this can be provided by addition of a cysteine residue). These reagents create a disulfide linkage between themselves and peptide cysteine residues on one protein and an amide linkage through the epsilon-amino on a lysine, or other free amino group in the other. A variety of such disulfide/amide-forming agents are known. See, for example, Immun Rev (1982) 62:185. Other bifunctional coupling agents form a thioether rather than a disulfide linkage. Many of these thio-ether-forming agents are commercially available and include reactive esters of 6-maleimidocaprioc acid, 2-bromoacetic acid, 2-iodoacetic acid, 4-N-maleimido-methyl)cyclohexane-1-carboxylic acid, and the like. The carboxyl groups can be activated by combining them with succinimide or 1-hydroxyl-2 nitro-4-sulfonic acid, sodium salt.
- Additional methods of coupling antigens employs the rotavirus/"binding peptide" system described in EPO Pub. No. 259,149, the disclosure of which is incorporated herein by reference. The foregoing list is not meant to be exhaustive, and modifications of the named compounds can clearly be used.

Any carrier may be used which does not itself induce the production of antibodies harmful to the

- 29 -

host. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins; polysaccharides, such as latex functionalized Sepharose, agarose, cellulose, cellulose beads and the like; polymeric amino acids, such as polyglutamic acid, polylysine, and the like; amino acid copolymers; and inactive virus particles. Especially useful protein substrates are serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, and other proteins well known to those skilled in the art.

Peptides comprising HCV amino acid sequences encoding at least one viral epitope derived from the NS5, envelope 1, and core region are useful immunological reagents. The 5'UT region is not known to be translated. For example, peptides comprising such truncated sequences can be used as reagents in an immunoassay. These peptides also are candidate subunit antigens in compositions for antiserum production or vaccines. While the truncated sequences can be produced by various known treatments of native viral protein, it is generally preferred to make synthetic or recombinant peptides comprising HCV sequence. Peptides comprising these truncated HCV sequences can be made up entirely of HCV sequences (one or more epitopes, either contiguous or noncontiguous), or HCV sequences and heterologous sequences in a fusion protein. Useful

SUBSTITUTE SHEET

- 30 -

heterologous sequences include sequences that provide for secretion from a recombinant host, enhance the immunological reactivity of the HCV epitope(s), or facilitate the coupling of the polypeptide to an immunoassay support or a vaccine carrier. See, E.G., EPO Pub. No. 116,201; U.S. Pat. No. 4,722,840; EPO Pub. No. 259,149; U.S. Pat. No. 4,629,783.

The size of peptides comprising the truncated HCV sequences can vary widely, the minimum size being a sequence of sufficient size to provide an HCV epitope, while the maximum size is not critical. For convenience, the maximum size usually is not substantially greater than that required to provide the desired HCV epitopes and function(s) of the heterologous sequence, if any. Typically, the truncated HCV amino acid sequence will range from about 5 to about 100 amino acids in length. More typically, however, the HCV sequence will be a maximum of about 50 amino acids in length, preferably a maximum of about 30 amino acids. It is usually desirable to select HCV sequences of at least about 10, 12 or 15 amino acids, up to a maximum of about 20 or 25 amino acids.

HCV amino acid sequences comprising epitopes can be identified in a number of ways. For example, the entire protein sequence corresponding to each of the NS5, envelope 1, and core regions can be screened by preparing a series of short peptides that together span

SUBSTITUTE SHEET

- 31 -

the entire protein sequence of such regions. By starting with, for example, peptides of approximately 100 amino acids, it would be routine to test each peptide for the presence of epitope(s) showing a
5 desired reactivity, and then testing progressively smaller and overlapping fragments from an identified peptides of 100 amino acids to map the epitope of interest. Screening such peptides in an immunoassay is within the skill of the art. It is also known to carry
10 out a computer analysis of a protein sequence to identify potential epitopes, and then prepare peptides comprising the identified regions for screening.

The immunogenicity of the epitopes of HCV may also be enhanced by preparing them in mammalian or yeast
15 systems fused with or assembled with particle-forming proteins such as, for example, that associated with hepatitis B surface antigen. See, e.g., US 4,722,840. Constructs wherein the HCV epitope is linked directly to the particle-forming protein coding sequences
20 produce hybrids which are immunogenic with respect to the HCV epitope. In addition, all of the vectors prepared include epitopes specific to HBV, having various degrees of immunogenicity, such as, for example, the pre-S peptide. Thus, particles
25 constructed from particle forming protein which include HCV sequences are immunogenic with respect to HCV and HBV.

SUBSTITUTE SHEET

- 32 -

Hepatitis surface antigen (HBSAg) has been shown to be formed and assembled into particles in S. cerevisiae (P. Valenzuela et al. (1982)), as well as in, for example, mammalian cells (P. Valenzuela et al. 5 1984)). The formation of such particles has been shown to enhance the immunogenicity of the monomer subunit. The constructs may also include the immunodominant epitope of HBSAg, comprising the 55 amino acids of the presurface (pre-S) region. Neurath et al. (1984). 10 Constructs of the pre-S-HBSAg particle expressible in yeast are disclosed in EPO 174,444, published March 19, 1986; hybrids including heterologous viral sequences for yeast expression are disclosed in EPO 175,261, published March 26, 1966. These constructs may also be 15 expressed in mammalian cells such as Chinese hamster ovary (CHO) cells using an SV40-dihydrofolate reductase vector (Michelle et al. (1984)).

In addition, portions of the particle-forming protein coding sequence may be replaced with codons 20 encoding an HCV epitope. In this replacement, regions which are not required to mediate the aggregation of the units to form immunogenic particles in yeast of mammals can be deleted, thus eliminating additional HBV antigenic sites from competition with the HCV epitope.

25

Vaccines

Vaccines may be prepared from one or more

SUBSTITUTE SHEET

- 33 -

immunogenic peptides derived from HCV. The observed
homology between HCV and Flaviviruses provides
information concerning the peptides which are likely to
be most effective as vaccines, as well as the regions
5 of the genome in which they are encoded.

Multivalent vaccines against HCV may be comprised
of one or more epitopes from one or more proteins
derived from the NS5, envelope 1, and core regions. In
particular, vaccines are contemplated comprising one or
10 more HCV proteins or subunit antigens derived from the
NS5, envelope 1, and core regions. The 5'UT region is
not known to be translated.

The preparation of vaccines which contain an
immunogenic peptide as an active ingredient, is known
15 to one skilled in the art. Typically, such vaccines
are prepared as injectables, either as liquid solutions
or suspensions; solid forms suitable for solution in,
or suspension in, liquid prior to injection may also be
prepared. The preparation may also be emulsified, or
20 the protein encapsulated in liposomes. The active
immunogenic ingredients are often mixed with excipients
which are pharmaceutically acceptable and compatible
with the active ingredient. Suitable excipients are,
for example, water, saline, dextrose, glycerol,
25 ethanol, or the like and combinations thereof. In
addition, if desired, the vaccine may contain minor
amounts of auxiliary substances such as wetting or

SUBSTITUTE SHEET

- 34 -

- emulsifying agents, pH buffering agents, and/or adjuvants which enhance the effectiveness of the vaccine. Examples of adjuvants which may be effective include but are not limited to: aluminum hydroxide,
- 5 N-acetyl-muramyl-L-theronyl-D- isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl- D-isoglutamine (CGP 11637, referred to as nor-MDP), N- acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1- 2-dipalmitoyl -sn-glycero-3-hydroxyphosphoryloxy)- ethylamine (CGP
- 10 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. The effectiveness of an adjuvant may be
- 15 determined by measuring the amount of antibodies directed against an immunogenic peptide containing an HCV antigenic sequence resulting from administration of this peptide in vaccines which are also comprised of the various adjuvants.
- 20 The vaccines are conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, in some
- 25 cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such

SUBSTITUTE SHEET

- 35 -

suppositories may be formed from mixtures containing the active ingredient in the range of 0/5% to 10%, preferably 1%-2%. Oral formulations include such normally employed excipients as, for example,

5 pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

The examples below are provided for illustrative purposes and are not intended to limit the scope of the

10 present invention.

I. Detection of HCV RNA from Serum

RNA was extracted from serum using guanidinium salt, phenol and chloroform according to the

15 instructions of the kit manufacturer (RNAzol™ B kit, Cinna/Biotechx). Extracted RNA was precipitated with isopropanol and washed with ethanol. A total of 25 µl serum was processed for RNA isolation, and the purified RNA was resuspended in 5 µl diethyl

20 pyrocarbonate treated water for subsequent cDNA synthesis.

II. cDNA Synthesis and Polymerase Chain Reaction (PCR)
Amplification

25 Table 1 lists the sequence and position (with reference to HCV1) of all the PCR primers and probes used in these examples. Letter designations for

SUBSTITUTE SHEET

- 36 -

nucleotides are consistent with 37 C.F.R. §§1.821-1.825. Thus, the letters A, C, G, T, and U are used in the ordinary sense of adenine, cytosine, guanine, thymine, and uracil. The letter M means A or C; R means A or G; W means A or T/U; S means C or G; Y means C or T/U; K means G or T/U; V means A or C or G, not T/U; H means A or C or T/U, not G; D means A or G or T/U, not C; B means C or G or T/U, not A; N means (A or C or G or T/U) or (unknown or other). Table 1 is set forth below:

Table 1

Seq. No.	Sequence (5'-3')	Nucleotide Position
	=====	
	67 CAAACGTAACACCAACCGRCGCCACAGG	374-402
15	68 ACAGAYCCGCAKAGRTCCCCCAG	1192-1169
	69 GCAACCTCGAGGTAGACGTCAGCCTATCCC	509-538
	70 GCAACCTCGTGGAAGGCGACAACCTATCCC	509-538
	71 GTCACCAATGATTGCCCTAACTCGAGTATT	948-977
	72 GTCACGAACGACTGCTCCA ACTCAAG	948-973
20	73 TGGACATGATCGCTGGWGCYCACTGGGG	1375-1402
	74 TGGAYATGGTGGYGGGGGCYCACTGGGG	1375-1402
	75 ATGATGAACTGGTCVCCYAC	1308-1327
	76 ACCTTVGCCCAGTTSCC RC CATGGA	1453-1428
	77 AACCCTCTATGYCCGGYCAT	205-226
25	78 GAATCGCTGGGGTGACCG	171-188
	79 CCATGAATCACTCCCCTGTGAGGA ACTA	30-57
	80 TTGCGGGGGCACGCCCAA	244-227

SUBSTITUTE SHEET

- 37 -

For cDNA synthesis and PCR amplification, a protocol developed by Perkin-Elmer/Cetus (GeneAmp® RNA PCR kit) was used. Both random hexamer and primers with specific complementary sequences to HCV were employed to prime the reverse transcription (RT) reaction. All processes, except for adding and mixing reaction components, were performed in a thermal cycler (MJ Research, Inc.). The first strand cDNA synthesis reaction was inactivated at 99°C for 5 min, and then cooled at 50°C for 5 min before adding reaction components for subsequent amplification. After an initial 5 cycles of 97°C for 1 min, 50°C for 2 min, and 72°C for 3 min, 30 cycles of 94°C for 1 min, 55°C for 2 min, and 72°C for 3 min followed, and then a final 7 min of elongation at 72°C.

For the genotyping analysis, sequences 67 and 68 were used as primers in the PCR reaction. These primers amplify a segment corresponding to the core and envelope regions. After amplification, the reaction products were separated on an agarose gel and then transferred to a nylon membrane. The immobilized reaction products were allowed to hybridize with a ³²P-labelled nucleic acid corresponding to either Genotype I (core or envelope 1) or Genotype II (core or envelope 1). Nucleic acid corresponding to Genotype 1 comprised sequences numbered 69 (core), 71 (envelope), and 73 (envelope). Nucleic acid corresponding to

SUBSTITUTE SHEET

- 38 -

Genotype II comprised sequences numbered 70 (core), 72 (envelope), and 74 (envelope).

The Genotype I probes only hybridized to the product amplified from isolates which had Genotype I sequence. Similarly, Genotype II probes only hybridized to the product amplified from isolates which had Genotype II sequence.

In another experiment, PCR products were generated using sequences 79 and 80. The products were analyzed as described above except Sequence No. 73 was used to detect Genotype I, Sequence No. 74 was used to detect Genotype II, Sequence No. 77 (5'UT) was used to detect Genotype III, and Sequence No. 78 (5'UT) was used to detect Genotype IV. Each sequence hybridized in a genotype specific manner.

III. Detection of HCV GI-GIV using a sandwich hybridization assay for HCV RNA

An amplified solution phase nucleic acid sandwich hybridization assay format is described in this example. The assay format employs several nucleic acid probes to effect capture and detection. A capture probe nucleic acid is capable of associating a complementary probe bound to a solid support and HCV nucleic acid to effect capture. A detection probe nucleic acid has a first segment (A) that binds to HCV nucleic acid and a second segment (B) that hybridizes to a second amplifier nucleic acid.

- 39 -

The amplifier nucleic acid has a first segment (B*) that hybridizes to segment (B) of the probe nucleic acid and also comprises fifteen iterations of a segment (C). Segment C of the amplifier nucleic acid is
 5 capable of hybridizing to three labeled nucleic acids.

Nucleic acid sequences which correspond to nucleotide sequences of the envelope 1 gene of Group I HCV isolates are set forth in sequences numbered 81-99. Table 2 sets forth the area of the HCV genome
 10 to which the nucleic acid sequences correspond and a preferred use of the sequences.

Table 2

15	Probe Type	Sequence No.	Complement of Nucleotide Numbers
=====			
	Label	81	879-911
	Label	82	912-944
	Capture	83	945-977
20	Label	84	978-1010
	Label	85	1011-1043
	Label	86	1044-1076
	Label	87	1077-1109
	Capture	88	1110-1142
25	Label	89	1143-1175

SUBSTITUTE SHEET

- 40 -

Table 2 continued

	Probe Type	Sequence No.	Complement of Nucleotide Numbers
5	=====		
	Label	90	1176-1208
	Label	91	1209-1241
	Label	92	1242-1274
	Capture	93	1275-1307
10	Label	94	1308-1340
	Label	95	1341-1373
	Label	96	1374-1406
	Label	97	1407-1439
	Capture	98	1440-1472
15	Label	99	1473-1505

Nucleic acid sequences which correspond to
 nucleotide sequences of the envelope 1 gene of Group II
 HCV isolates are set forth in sequences 100-118. Table
 20 3 sets forth the area of the HCV genome to which the
 nucleic acid corresponds and the preferred use of the
 sequences.

SUBSTITUTE SHEET

- 41 -

Table 3

	Probe Type	Sequence No.	Complement of Nucleotide Numbers
5	=====		
	Label	100	879-911
	Label	101	912-944
	Capture	102	945-977
	Label	103	978-1010
10	Label	104	1011-1043
	Label	105	1044-1076
	Label	106	1077-1109
	Capture	107	1110-1142
	Label	108	1143-1175
15	Label	109	1176-1208
	Label	110	1209-1241
	Label	111	1242-1274
	Capture	112	1275-1307
	Label	113	1308-1340
20	Label	114	1341-1373
	Label	115	1374-1406
	Label	116	1407-1439
	Capture	117	1440-1472
	Label	118	1473-1505

25

Nucleic acid sequences which correspond to
nucleotide sequences in the C gene and the 5'UT region

SUBSTITUTE SHEET

- 42 -

are set forth in sequences 119-145. Table 4 identifies the sequence with a preferred use.

Table 4

	Probe Type	Sequence No.
	=====	=====
	Capture	119
	Label	120
5		
	Label	121
	Label	122
10	Capture	123
	Label	124
	Label	125
15	Label	126
	Capture	127
	Label	128
	Label	129
	Label	130
20	Capture	131
	Label	132
	Label	133
	Label	134
	Label	135
25	Capture	136
	Label	137
	Label	138

SUBSTITUTE SHEET

- 43 -

Table 4 continued

	Probe Type	Sequence No.
	=====	=====
5	Label	139
	Capture	140
	Label	141
	Label	142
	Label	143
10	Capture	144
	Label	145

The detection and capture probe HCV-specific segments, and their respective names as used in this assay were as follows.

- 15 Capture sequences are sequences numbered 119-122 and 141-144.
 Detection sequences are sequences numbered 119-140.

- 20 Each detection sequence contained, in addition to the sequences substantially complementary to the HCV sequences, a 5' extension (B) which extension (B) is complementary to a segment of the second amplifier nucleic acid. The extension (B) sequence is identified in the Sequence Listing as Sequence No. 146, and is
 25 reproduced below.

AGGCATAGGACCCGTGTCTT

SUBSTITUTE SHEET

- 44 -

Each capture sequence contained, in addition to the sequences substantially complementary to HCV sequences, a sequence complementary to DNA bound to a solid phase. The sequence complementary to DNA bound to a solid support was carried downstream from the capture sequence. The sequence complementary to the DNA bound to the support is set forth as Sequence No. 147 and is reproduced below.

CTTCTTTGGAGAAAGTGGTG

10 Microtiter plates were prepared as follows. White Microlite 1 Removawell strips (polystyrene microtiter plates, 96 wells/plate) were purchased from Dynatech Inc.

15 Each well was filled with 200 μ l 1 N HCl and incubated at room temperature for 15-20 min. The plates were then washed 4 times with 1X PBS and the wells aspirated to remove liquid. The wells were then filled with 200 μ l 1 N NaOH and incubated at room temperature for 15-20 min. The plates were again washed 4 times with 1X PBS and the wells aspirated to remove liquid.

25 Poly(phe-lys) was purchased from Sigma Chemicals, Inc. This polypeptide has a 1:1 molar ratio of phe:lys and an average m.w. of 47,900 gm/mole. It has an average length of 309 amino acids and contains 155 amines/mole. A 1 mg/ml solution of the polypeptide was mixed with 2M NaCl/1X PBS to a final concentration of

SUBSTITUTE SHEET

- 45 -

0.1 mg/ml (pH 6.0). A volume of 200 μ l of this solution was added to each well. The plate was wrapped in plastic to prevent drying and incubated at 30°C overnight. The plate was then washed 4 times with 1X PBS and the wells aspirated to remove liquid.

5 The following procedure was used to couple the nucleic acid, a complementary sequence to Sequence No. 147, to the plates, hereinafter referred to as immobilized nucleic acid. Synthesis of immobilized nucleic acid having a sequence complementary to
10 Sequence No. 133 was described in EPA 883096976. A quantity of 20 mg disuccinimidyl suberate was dissolved in 300 μ l dimethyl formamide (DMF). A quantity of 26 OD₂₆₀ units of immobilized nucleic acid was added to
15 100 μ l coupling buffer (50 mM sodium phosphate, pH 7.8). The coupling mixture was then added to the DSS-DMF solution and stirred with a magnetic stirrer for 30 min. An NAP-25 column was equilibrated with 10 mM sodium phosphate, pH 6.5. The coupling mixture
20 DSS-DMF solution was added to 2 ml 10 mM sodium phosphate, pH 6.5, at 4°C. The mixture was vortexed to mix and loaded onto the equilibrated NAP-25 column. DSS-activated immobilized nucleic acid DNA was eluted from the column with 3.5 ml 10 mM sodium phosphate, pH
25 6.5. A quantity of 5.6 OD₂₆₀ units of eluted DSS-activated immobilized nucleic acid DNA was added to 1500 ml 50 mM sodium phosphate, pH 7.8. A volume of 50

SUBSTITUTE SHEET

- 46 -

µl of this solution was added to each well and the plates were incubated overnight. The plate was then washed 4 times with 1X PBS and the wells aspirated to remove liquid.

- 5 Final stripping of plates was accomplished as follows. A volume of 200 µl of 0.2N NaOH containing 0.5% (w/v) SDS was added to each well. The plate was wrapped in plastic and incubated at 65°C for 60 min. The plate was then washed 4 times with 1X PBS and the
10 wells aspirated to remove liquid. The stripped plate was stored with desiccant beads at 2-8°C.

Serum samples to be assayed were analyzed using PCR followed by sequence analysis to determine the genotype.

- 15 Sample preparation consisted of delivering 50 µl of the serum sample and 150 µl P-K Buffer (2 mg/ml proteinase K in 53 mM Tris-HCl, pH 8.0/0.6 M NaCl/0.06 M sodium citrate/8 mM EDTA, pH 8.0/1.3%SDS/16µg/ml
20 sonicated salmon sperm DNA/7% formamide/50 fmoles capture probes/160 fmoles detection probes) to each well. Plates were agitated to mix the contents in the well, covered and incubated for 16 hr at 62°C.

- After a further 10 minute period at room temperature, the contents of each well were aspirated
25 to remove all fluid, and the wells washed 2X with washing buffer (0.1% SDS/0.015 M NaCl/ 0.0015 M sodium citrate). The amplifier nucleic acid was then added to

SUBSTITUTE SHEET

- 47 -

each well (50 μ l of 0.7 fmole/ μ l solution in 0.48 M NaCl/0.048 M sodium citrate/0.1% SDS/0.5% "blocking reagent" (Boehringer Mannheim, catalog No. 1096 176)). After covering the plates and agitating to mix the contents in the wells, the plates were incubated for 30 min. at 52°C.

After a further 10 min period at room temperature, the wells were washed as described above.

Alkaline phosphatase label nucleic acid, disclosed in EP 883096976, was then added to each well (50 μ l/well of 2.66 fmoles/ μ l). After incubation at 52°C for 15 min., and 10 min. at room temperature, the wells were washed twice as above and then 3X with 0.015 M NaCl/0.0015 M sodium citrate.

An enzyme-triggered dioxetane (Schaap et al., Tet. Lett. (1987) 28:1159-1162 and EPA Pub. No. 0254051), obtained from Lumigen, Inc., was employed. A quantity of 50 μ l Lumiphos 530 (Lumigen) was added to each well. The wells were tapped lightly so that the reagent would fall to the bottom and gently swirled to distribute the reagent evenly over the bottom. The wells were covered and incubated at 37°C for 20-40 min.

Plates were then read on a Dynatech ML 1000 luminometer. Output was given as the full integral of the light produced during the reaction.

The assay positively detected each of the serum samples, regardless of genotype.

SUBSTITUTE SHEET

- 48 -

IV. Expression of the Polypeptide Encoded in Sequences Defined by Differing Genotypes

HCV polypeptides encoded by a sequence within sequences 1-66 are expressed as a fusion polypeptide with superoxide dismutase (SOD). A cDNA carrying such sequences is subcloned into the expression vector pSODcfl (Steimer et al. 1986)).

First, DNA isolated from pSODcfl is treated with BamHI and EcoRI, and the following linker was ligated into the linear DNA created by the restriction enzymes:

5 GAT CCT GGA ATT CTG ATA AGA
CCT TAA GAC TAT TTT AA 3

After cloning, the plasmid containing the insert is isolated.

Plasmid containing the insert is restricted with EcoRI. The HCV cDNA is ligated into this EcoRI linearized plasmid DNA. The DNA mixture is used to transform E. coli strain D1210 (Sadler et al. (1980)). Polypeptides are isolated on gels.

20

V. Antigenicity of Polypeptides

The antigenicity of polypeptides formed in Section IV is evaluated in the following manner. Polyethylene pins arranged on a block in an 8 12 array (Coselco Mimetopes, Victoria, Australia) are prepared by placing the pins in a bath (20% v/v piperidine in dimethylformamide (DMF)) for 30 minutes at room

25

- 49 -

temperature. The pins are removed, washed in DMF for 5 minutes, then washed in methanol four times (2 min/wash). The pins are allowed to air dry for at least 10 minutes, then washed a final time in DMF (5Min). 1-Hydroxybenzotriazole (HOBt, 367 mg) is dissolved in DMF (80 μ L) for use in coupling Fmoc-protected polypeptides prepared in Section IV.

The protected amino acids are placed in micro-titer plate wells with HOBt, and the pin block placed over the plate, immersing the pins in the wells. The assembly is then sealed in a plastic bag and allowed to react at 25°C for 18 hours to couple the first amino acids to the pins. The block is then removed, and the pins washed with DMF (2 min.), MeOH (4 x, 2 min.), and again with DMF (2 min.) to clean and deprotect the bound amino acids. The procedure is repeated for each additional amino acid coupled, until all octamers are prepared.

The free N-termini are then acetylated to compensate for the free amide, as most of the epitopes are not found at the N-terminus and thus would not have the associated positive charge. Acetylation is accomplished by filling the wells of a microtiter plate with DMF/acetic anhydride/triethylamine (5:2:1 v/v/v) and allowing the pins to react in the wells for 90 minutes at 20°C. The pins are then washed with DMF (2

SUBSTITUTE SHEET

- 50 -

min.) and MeOH (4 x, 2 min.), and air dried for at least 10 minutes.

The side chain protecting groups are removed by treating the pins with trifluoroacetic acid/phenol/
5 dithioethane (95:2.5:1.5, v/v/v) in polypropylene bags for 4 hours at room temperature. The pins are then washed in dichloromethane (2 x, 2 min.), 5% di-isopropylethylamine/dichloromethane (2 x, 5 min.),
dichloromethane (5 min.), and air-dried for at least 10
10 minutes. The pins are then washed in water (2 min.), MeOH (18 hours), dried in vacuo, and stored in sealed plastic bags over silica gel. IV.B.15.b Assay of Peptides.

Octamer-bearing pins are treated by sonicating for
15 30 minutes in a disruption buffer (1% sodium dodecylsulfate, 0.1% 2-mercaptoethanol, 0.1 M NaH₂PO₄) at 60°C. The pins are then immersed several times in water (60°C), followed by boiling MeOH (2 min.), and allowed to air dry.

20 The pins are then precoated for 1 hour at 25°C in microtiter wells containing 200 µL blocking buffer (1% ovalbumin, 1% BSA, 0.1% Tween, and 0.05% NaN₃ in PBS), with agitation. The pins are then immersed in
25 microtiter wells containing 175 µL antisera obtained from human patients diagnosed as having HCV and allowed to incubate at 4°C overnight. The formation of a complex between polyclonal antibodies of the serum and

SUBSTITUTE SHEET

- 51 -

the polypeptide initiates that the peptides give rise to an immune response in vivo. Such peptides are candidates for the development of vaccines.

- Thus, this invention has been described and
- 5 illustrated. It will be apparent to those skilled in the art that many variations and modifications can be made without departing from the purview of the appended claims and without departing from the teaching and scope of the present invention.

SUBSTITUTE SHEET

- 52 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Tai-An Cha
- (ii) TITLE OF INVENTION: HCV GENOMIC SEQUENCES
 FOR DIAGNOSTICS AND THERAPEUTICS
- 10 (iii) NUMBER OF SEQUENCES: 147
- (iv) CORRESPONDENCE ADDRESS:
- (A) ADDRESSEE: Wolf, Greenfield & Sacks, P.C.
- (B) STREET: 600 Atlantic Avenue
- 15 (C) CITY: Boston
- (D) STATE: Massachusetts
- (E) COUNTRY: USA
- (F) ZIP: 02210
- 20 (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: Diskette, 5.25 inch
- (B) COMPUTER: IBM compatible
- (C) OPERATING SYSTEM: MS-DOS Version 3.3
- (D) SOFTWARE: WordPerfect 5.1

SUBSTITUTE SHEET

- 53 -

- 5 (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Not Available
(B) FILING DATE: Not Available
(C) CLASSIFICATION: Not Available
- (vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/697,326
(B) FILING DATE: 8 May 1991
- 10 (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Janiuk, Anthony J.
(B) REGISTRATION NUMBER: 29,809
(C) REFERENCE/DOCKET NUMBER: C0772/7000
- 15 (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 720-3500
(B) TELEFAX: (617) 720-2441
(C) TELEX: EZEKIEL
- 20 (2) INFORMATION FOR SEQ ID NO: 1:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
25 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 54 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE: (ATCC # 40394)

(C) INDIVIDUAL ISOLATE: ns5hcv1

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1

	CTCCACAGTC	ACTGAGAGCG	ACATCCGTAC	GGAGGAGGCA	40
	ATCTACCAAT	GTTGTGACCT	CGACCCCCAA	GCCCGCGTGG	80
	CCATCAAGTC	CCTCACCAG	AGGCTTTATG	TTGGGGGCCC	120
10	TCTTACCAAT	TCAAGGGGGG	AGAACTGCGG	CTATCGCAGG	160
	TGCCGCGCGA	GCGGCGTACT	GACAACTAGC	TGTGGTAACA	200
	CCCTCACTTG	CTACATCAAG	GCCCGGGCAG	CCTGTGCGAG	240
	CGCAGGGCTC	CAGGACTGCA	CCATGCTCGT	GTGTGGCGAC	280
	GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG	GTCCAGGAGG	320
15	ACGCGGCGAG	CCTGAGAGCC			340

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 55 -

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5i21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2

5	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA	40
	ATTTACCAAT GTTGTGACCT GGACCCCCAA GCCCGCATGG	80
	CCATCAAGTC CCTCACTGAG AGGCTTTATG TCGGGGGCCC	120
	TCTTACCAAT TCAAGGGGGG AGAACTGCGG CTACCGCAGG	160
	TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTGGTAACA	200
10	CCCTCACTTG CTACATCAAG GCCCGGGCAG CCTGTGCGAGC	240
	CGCAGGGGCTC CAGGACTGCA CCATGCTTGT GTGTGGCGAC	280
	GACTTAGTCG TTATCTGTGA AAGTGCGGGG GTCCAGGAGG	320
	ACGCGGCGAG CCTGAGAGCC	340

15 (2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) individual isolate: ns5pt1

SUBSTITUTE SHEET

- 56 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3

	CTCCACAGTC	ACTGAGAGCG	ACATCCGTAC	GGAGGAGGCA	40
	ATCTACCAAT	GTTGTGATCT	GGACCCCCAA	GCCCGCGTGG	80
	CCATCAAGTC	CCTCACTGAG	AGGCTTTACG	TTGGGGGCCC	120
5	TCTTACCAAT	TCAAGGGGGG	AGAAGTCCGG	CTACCGCAGG	160
	TGCCGGGCGA	GCGGCGTACT	GACAACTAGC	TGTGGTAATA	200
	CCCTCACTTG	CTACATCAAG	GCCCCGGGAG	CCTGTCGAGC	240
	CGCAGGGCTC	CGGGACTGCA	CCATGCTCGT	GTGTGGTGAC	280
	GACTTGGTCT	TTATCTGTGA	GAGTGCAGGG	GTCCAGGAGG	320
10	ACGCGGCGAG	CCTGAGAGCC			340

(2) INFORMATION FOR SEQ ID NO: 4

(i) SEQUENCE CHARACTERISTICS:

15	(A)	LENGTH:	340 nucleotides
	(B)	TYPE:	nucleic acid
	(C)	STRANDEDNESS:	single
	(D)	TOPOLOGY:	linear

20	(ii)	MOLECULE TYPE:	DNA
----	------	----------------	-----

(vi) ORIGINAL SOURCE:

	(C)	INDIVIDUAL ISOLATE:	ns5gm2
--	-----	---------------------	--------

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4

	CTCTACAGTC	ACTGAGAACG	ACATCCGTAC	GGAGGAGGCA	40
	ATTTACCAAT	GTTGTGACCT	GGACCCCCAA	GCCCGCGTGG	80

SUBSTITUTE SHEET

- 57 -

CCATCAAGTC CCTCACTGAG AGGCTTTATG TTGGGGGCCC 120
 CCTTACCAAT TCAAGGGGGG AAAACTGCGG CTATCGCAGG 160
 TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTGGTAACA 200
 CCCTCACTTG CTACATTAAG GCCCGGGCAG CCTGTCGAGC 240
 5 CGCAGGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC 280
 GACTTAGTCG TTATCTGTGA GAGTGCGGGA GTCCAGGAGG 320
 ACGCGGCGAA CTTGAGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 5

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

20

(C) INDIVIDUAL ISOLATE: ns5us17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5

25

CTCCACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA 40
 ATCTACCAAT GTTGTGACCT GGACCCCCAA GCCCGCGTGG 80
 CCATCAAGTC CCTCACCGAG AGGCTTTATG TCGGGGGCCC 120
 TCTTACCAAT TCAAGGGGGG AAAACTGCGG CTATCGCAGG 160
 TGCCGCGCAA GCGGCGTACT GACAACTAGC TGTGGTAACA 200

SUBSTITUTE SHEET

- 58 -

CCCTCACTTG TTACATCAAG GCCCAAGCAG CCTGTCGAGC 240
CGCAGGGCTC CGGGACTGCA CCATGCTCGT GTGTGGCGAC 280
GACTTAGTCG TTATCTGTGA AAGTCAGGGA GTCCAGGAGG 320
ATGCAGCGAA CCTGAGAGCC 340

5

(2) INFORMATION FOR SEQ ID NO: 6

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sp2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6

20 CTCTACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA 40
ATCTACCAAT GTTGTGACCT GGACCCCGAA GCCCGTGTGG 80
CCATCAAGTC CCTCACTGAG AGGCTTTATG TTGGGGGCCC 120
TCTTACCAAT TCAAGGGGGG AGAACTGCGG CTACCGCAGG 160
TGCCGCGCAA GCGGCGTACT GACGACTAGC TGTGGTAATA 200
25 CCCTCACTTG TTACATCAAG GCCCGGGCAG CCTGTCGAGC 240
CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC 280

SUBSTITUTE SHEET

- 59 -

GACCTAGTCG TTATCTGCGA AAGTGCGGGG GTCCAGGAGG 320
ACGCGGCGAG CCTGAGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 7

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

15

(C) INDIVIDUAL ISOLATE: ns5j1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7

CTCCACAGTC ACTGAGAATG ACACCCGTGT TGAGGAGTCA 40
ATTTACCAAT GTTGTGACTT GGCCCCCGAA GCCAGACAGG 80
20 CCATAAGGTC GCTCACAGAG CGGCTCTATG TCGGGGGTCC 120
TATGACTAAC TCCAAAGGGC AGAACTGCGG CTATCGCCGG 160
TGCCGCGCGA GCGGCGTGCT GACGACTAGC TGCGGTAATA 200
CCCTCACATG CTACCTGAAG GCCACAGCGG CCTGTCGAGC 240
TGCCAAGCTC CAGGACTGCA CGATGCTCGT GAACGGAGAC 280
25 GACCTTGTCG TTATCTGTGA AAGCGCGGGG AACCAAGAGG 320
ACGCGGCAAG CCTACGAGCC 340

SUBSTITUTE SHEET

- 60 -

(2) INFORMATION FOR SEQ ID NO: 8

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

- (C) INDIVIDUAL ISOLATE: ns5k1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8

15 CTCAACGGTC ACTGAGAATG ACATCCGTGT TGAGGAGTCA 40
ATTTACCAAA GTTGTGACTT GGCCCCCGAG GCCAGACAAG 80
CCATAAGGTC GCTCACAGAG CGGCTTTACA TCGGGGGCCC 120
CCTGACTAAT TCAAAAGGGC AGAACTGCGG CTATCGCCGA 160
TGCCGCGCCA GCGGTGTGCT GACGACTAGC TGCGGTAATA 200
20 CCCTCACATG TTA CTGTAAG GCCACTGCGG CCTGTAGAGC 240
TGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGCGGAGAC 280
GACCTTGTCG TTATCTGTGA AAGCGCGGGA ACCCAGGAGG 320
ATGCGGCGAG CCTACGAGTC 340

25 (2) INFORMATION FOR SEQ ID NO: 9

SUBSTITUTE SHEET

- 61 -

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10

(C) INDIVIDUAL ISOLATE: ns5k1.1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9

	CTCAACGGTC ACCGAGAATG ACATCCGTGT TGAGGAGTCA	40
	ATTTATCAAT GTTGTGCCTT GGCCCCCGAG GCTAGACAGG	80
15	CCATAAGGTC GCTCACAGAG CGGCTTTATA TCGGGGGCCC	120
	CCTGACCAAT TCAAAGGGGC AGAACTGCGG TTATCGCCGG	160
	TGCCGCGCCA GCGGCGTACT GACGACCAGC TGCGGTAATA	200
	CCCTTACATG TTA CT TGAAG GCCTCTGCAG CCTGTCGAGC	240
	CGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGTGGGGAC	280
20	GACCTTGTCG TTATCTGTGA AAGCGCGGGA ACCCAGGAGG	320
	ACGCGGCGAA CCTACGAGTC	340

(2) INFORMATION FOR SEQ ID NO: 10

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid

SUBSTITUTE SHEET

- 62 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5gh6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10

10	CTCAACGGTC ACTGAGAGTG ACATCCGTGT CGAGGAGTCG	40
	ATTTACCAAT GTTGTGACTT GGCCCCCGAA GCCAGGCAGG	80
	CCATAAGGTC GCTCACCGAG CGACTTTATA TCGGGGGCCC	120
	CCTGACTAAT TCAAAAGGGC AGAACTGCGG TTATCGCCGG	160
	TGCCGCGCGA GCGGCGTGCT GACGACTAGC TGC GGTAATA	200
15	CCCTCACATG TTA CTTGAAG GCCTCTGCAG CCTGTCGAGC	240
	TGCAAAGCTC CAGGACTGCA CGATGCTCGT GAACGGGGAC	280
	GACCTTGTCG TTATCTGCGA GAGCGCGGGA ACCCAAGAGG	320
	ACGCGGCGAG CCTACGAGTC	340

20 (2) INFORMATION FOR SEQ ID NO: 11

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

25 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 63 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5spl

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11

	CTCCACAGTC	ACTGAGAGTG	ACATCCGTGT	TGAGGAGTCA	40
	ATTTACCAAT	GTTGTGACTT	GGCCCCCGAA	GCCAGACAGG	80
	CTATAAGGTC	GCTCACAGAG	CGGCTGTACA	TCGGGGGTCC	120
10	CCTGACTAAT	TCAAAGGGC	AGAACTGCGG	CTATCGCCGG	160
	TGCCGCGCAA	GCGGCGTGCT	GACGACTAGC	TGCGGTAACA	200
	CCCTCACATG	TTACTTGAAG	GCCTCTGCGG	CCTGTGCGAGC	240
	TGCGAAGCTC	CAGGACTGCA	CGATGCTCGT	GTGCGGTGAC	280
	GACCTTGTCG	TTATCTGTGA	GAGCGCGGGA	ACCCAAGAGG	320
15	ACGCGGCGAG	CCTACGAGTC			340

(2) INFORMATION FOR SEQ ID NO: 12

(i) SEQUENCE CHARACTERISTICS:

20	(A)	LENGTH: 340 nucleotides
	(B)	TYPE: nucleic acid
	(C)	STRANDEDNESS: single
	(D)	TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 64 -

(C) individual isolate: ns5sp3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12

	CTCAACAGTC	ACTGAGAGTG	ACATCCGTGT	TGAGGAGTCA	40
5	ATCTACCAAT	GTTGTGACTT	GGCCCCCGAA	GCCAGACAGG	80
	CTATAAGGTC	GCTCACAGAG	CGGCTTTACA	TCGGGGGTCC	120
	CCTGACTAAT	TCAAAAGGGC	AGAACTGCGG	CTATCGCCGG	160
	TGCCGCGCAA	GCGGCGTGCT	GACGACTAGC	TGCGGTAATA	200
	CCCTCACATG	TTACCTGAAG	GCCAGTGCGG	CCTGTCGAGC	240
10	TGCGAAGCTC	CAGGACTGCA	CAATGCTCGT	GTGCGGTGAC	280
	GACCTTGTCG	TTATCTGTGA	GAGCGCGGGG	ACCCAAGAGG	320
	ACGCGGCGAG	CCTACGAGTC			340

(2) INFORMATION FOR SEQ ID NO: 13

15

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

25

(C) INDIVIDUAL ISOLATE: ns5k2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13

SUBSTITUTE SHEET

- 65 -

5 CTCAACCGTC ACTGAGAGAG ACATCAGAAC TGAGGAGTCC 40
 ATATAACCGAG CCTGCTCCCT GCCTGAGGAG GCTCACATTG 80
 CCATACACTC GCTGACTGAG AGGCTCTACG TGGGAGGGCC 120
 CATGTTCAAC AGCAAGGGCC AGACCTGCGG GTACAGGCGT 160
 TGCCGCGCCA GCGGGGTGCT CACCACTAGC ATGGGGAACA 200
 CCATCACATG CTATGTAAAA GCCCTAGCGG CTTGCAAGGC 240
 TGCAGGGATA GTTGCAACCCT CAATGCTGGT ATGCGGCGAC 280
 GACTTAGTTG TCATCTCAGA AAGCCAGGGG ACTGAGGAGG 320
 ACGAGCGGAA CCTGAGAGCT 340

10

(2) INFORMATION FOR SEQ ID NO: 14

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5arg8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14

25 CTCTACAGTC ACGTAAAAGG ACATCACATC CTAGGAGTCC 40
 ATCTACCACT CCTGTTCACT GCCCGAGGAG GCTCGAACTG 80
 CTATACACTC ACTGACTGAG AGACTATACG TAGGGGGGCC 120

SUBSTITUTE SHEET

- 66 -

CATGACAAAC AGCAAGGGGCC AATCCTGCGG GTACAGGCGT 160
 TGCCGCGCGA GCGCAGTGCT CACCACCAGC ATGGGCAACA 200
 CACTCACGTG CTACGTAAAA GCCAGGGCGG CGTGTAACGC 240
 CGCGGGGATT GTTGCTCCCA CCATGCTGGT GTGCGGTGAC 280
 5 GACCTGGTCG TCATCTCAGA GAGTCAAGGG GCTGAGGAGG 320
 ACGAGCAGAA CCTGAGAGTC 340

(2) INFORMATION FOR SEQ ID NO: 15

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5i10

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15

CTCTACAGTC ACAGAGAGGG ACATCAGAAC CGAGGAGTCC 40
 ATCTATCTGT CCTGCTCACT GCCTGAGGAG GCCCGAACTG 80
 CTATACACTC ACTGACTGAG AGACTGTACG TAGGGGGGCC 120
 25 CATGACAAAC AGCAAGGGGC AATCCTGCGG GTACAGGCGT 160
 TGCCGCGCGA GCGGAGTGCT CACCACCAGC ATGGGCAACA 200
 CGCTCACGTG CTACGTGAAA GCCAGAGCGG CGTGTAACGC 240

SUBSTITUTE SHEET

- 67 -

CGCGGGCATT GTTGCTCCCA CCATGTTGGT GTGCGGCGAC 280
 GACCTGGTTG TCATCTCAGA GAGTCAGGGG GTCGAGGAAG 320
 ATGAGCGGAA CCTGAGAGTC 340

5 (2) INFORMATION FOR SEQ ID NO: 16

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 10 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5arg6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16

CTCTACAGTC ACGGAGAGGG ACATCAGAAC CGAGGAGTCC 40
 20 ATCTATCTGT CCTGTTCACT GCCTGAGGAG GCTCGAACTG 80
 CCATACACTC ACTGACTGAG AGGCTGTACG TAGGGGGGCC 120
 CATGACAAAC AGCAAAGGGC AATCCTGCGG GTACAGGCGT 160
 TGCCGCGCGA GCGGAGTGCT CACCACCAGC ATGGGTAACA 200
 CACTCACGTG CTACGTGAAA GCTAAAGCGG CATGTAACGC 240
 25 CGCGGGCATT GTTGCCCCCA CCATGTTGGT GTGCGGCGAC 280
 GACCTAGTCG TCATCTCAGA GAGTCAAGGG GTCGAGGAGG 320
 ATGAGCGAAA CCTGAGAGCT 340

SUBSTITUTE SHEET

- 68 -

(2) INFORMATION FOR SEQ ID NO: 17

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5k2b

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17

15 CTCAACCGTC ACGGAGAGGG ACATAAGAAC AGAAGAATCC 40
ATATATCAGG GTTGTTCCTT GCCTCAGGAG GCTAGAACTG 80
CTATCCACTC GCTCACTGAG AGACTCTACG TAGGAGGGCC 120
CATGACAAAC AGCAAGGGAC AATCCTGCGG TTACAGGCGT 160
TGCCGCGCCA GCGGGGTCTT CACCACCAGC ATGGGGAATA 200
20 CCATGACATG CTACATCAA GCCCTTGACG CGTGCAAAGC 240
TGCAGGGATC GTGGACCCTA TCATGCTGGT GTGTGGAGAC 280
GACCTGGTCG TCATCTCGGA GAGCGAAGGT AACGAGGAGG 320
ACGAGCGAAA CCTGAGAGCT 340

25 (2) INFORMATION FOR SEQ ID NO: 18

(i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 69 -

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sa283

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18

CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCT	40
ATTTACCAAT CATTGTACTT GCAGCCTGAG GCGCGTGTGG	80
CAATACGGTC ACTCACCCAA CGCCTGTACT GTGGAGGCCC	120
CATGTATAAC AGCAAGGGGC AACAATGTGG TTATCGTAGA	160
TGCCGCGCCA GCGGCGTCTT CACCACTAGT ATGGGCAACA	200
CCATGACGTG CTACATTAAG GCTTTAGCCT CCTGTAGAGC	240
CGCAAAGCTC CAGGACTGCA CGCTCCTGGT GTGTGGTGAT	320
GATAAAGCGA CCTGAGAGCC	340

20

(2) INFORMATION FOR SEQ ID NO: 19

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

SUBSTITUTE SHEET

- 70 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sa156

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19

	CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCC	40
	ATTTACCAAT CATTGTACTT GCAGCCTGAG GCACGCGCGG	80
	CAATACGGTC ACTCACCCAA CGCCTGTACT GTGGAGGCCC	120
10	CATGTATAAC AGCAAGGGGC AACAATGTGG TTACCGTAGA	160
	TGCCGCGCCA GCGGCGTCTT CACCACCAGT ATGGGCAACA	200
	CCATGACGTG CTACATCAAG GCTTCAGCCG CCTGTAGAGC	240
	TGCAAAGCTC CAGGACTGCA CGCTCCTGGT GTGTGGTGTG	280
	ACCTTGGTGG CCATTGCGA GAGCCAAGGG ACGCACGAGG	320
15	ATGAAGCGTG CCTGAGAGTC	340

(2) INFORMATION FOR SEQ ID NO: 20

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 71 -

(C) INDIVIDUAL ISOLATE: ns5i11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20

	CTCTACTGTC	ACTGAACAGG	ACATCAGGGT	GGAAGAGGAG	40
5	ATATACCACT	GCTGTAACCT	TGAACCGGAG	GCCAGGAAAG	80
	TGATCTCCTC	CCTCACGGAG	CGGCTTTACT	GCGGGGGCCC	120
	TATGTTCAAC	AGCAAGGGGG	CCCAGTGTGG	TTATCGCCGT	160
	TGCCGTGCTA	GTGGAGTCCT	GCCTACCAGC	TTCGGCAACA	200
	CAATCACTTG	TTACATCAAG	GCTAGAGCGG	CTTCGAAGGC	240
10	CGCAGGCCTC	CGGAACCCGG	ACTTTCTTGT	CTGCGGAGAT	280
	GATCTGGTCG	TGGTGGCTGA	GAGTGATGGC	GTCGACGAGG	320
	ATAGAGCAGC	CCTGAGAGCC			340

(2) INFORMATION FOR SEQ ID NO: 21

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

25

(C) INDIVIDUAL ISOLATE: ns5i14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21

SUBSTITUTE SHEET

- 72 -

CTCGACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG 40
 ATATACCAAT GCTGTAACCT TGAACCGGAG GCCAGGAAAG 80
 TGATCTCCTC CCTCACGGAG CGGCTTTACT GCGGGGGCCC 120
 TATGTTCAAT AGCAAGGGGG CCCAGTGTGG TTATCGCCGT 160
 5 TGCCGTGCTA GTGGAGTTCT GCCTACCAGC TTCGGCAACA 200
 CAATCACTTG TTACATCAAG GCTAGAGCGG CTGCGAAGGC 240
 CGCAGGGCTC CGGACCCCGG ACTTTCTCGT CTGCGGAGAT 280
 GATCTGGTTG TGGTGGCTGA GAGTGATGGC GTCGACGAGG 320
 ATAGAACAGC CCTGCGAGCC 340

10

(2) INFORMATION FOR SEQ ID NO: 22

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5gh8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22

25 CTCAACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG 40
 ATATACCAAT GCTGTAACCT TGAACCGGAG GCCAGGAAAG 80
 TGATCTCCTC CCTCACGGAA CGGCTTTACT GCGGGGGCCC 120

SUBSTITUTE SHEET

- 73 -

5 TATGTTCAAC AGCAAGGGGG CCCAGTGTGG TTATCGCCGT 160
 TGCCGTGCCA GTGGAGTTCT GCCTACCAGC TTCGGCAACA 200
 CAATCACTTG TTACATCAAA GCTAGAGCGG CTGCCGAAGC 240
 CGCAGGCCTC CGGAACCCGG ACTTTCTTGT CTGCGGAGAT 280
 GATCTGGTTG TGGTGGCTGA GAGTGATGGC GTCAATGAGG 320
 ATAGAGCAGC CCTGGGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 23

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

- (vi) ORIGINAL SOURCE: (ATCC # 40394)
 (C) INDIVIDUAL ISOLATE: hcv1

20

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23
 GACGGCGTTG GTAATGGCTC AGCTGCTCCG GATCCCACAA 40
 GCCATCTTGG ACATGATCGC TGGTGCTCAC TGGGGAGTCC 80
 TGGCGGGCAT AGCGTATTTTC 100

25

(2) INFORMATION FOR SEQ ID NO: 24

SUBSTITUTE SHEET

- 74 -

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10

- (C) INDIVIDUAL ISOLATE: US5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24

GACGGCGTTG GTGGTAGCTC AGGTACTCCG GATCCCACAA 40

GCCATCATGG ACATGATCGC TGGAGCCCCAC TGGGGAGTCC 80

15

TGGCGGGCAT AGCGTATTTC 100

(2) INFORMATION FOR SEQ ID NO: 25

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 75 -

(C) INDIVIDUAL ISOLATE: AUS5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25

	AACGGCGCTG GTAGTAGCTC AGCTGCTCAG GGTCCCGCAA	40
5	GCCATCGTGG ACATGATCGC TGGTGCCAC TGGGGAGTCC	80
	TAGCGGGCAT AGCGTATTTT	100

(2) INFORMATION FOR SEQ ID NO: 26

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: US4

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26

	GACAGCCCTA GTGGTATCGC AGTTACTCCG GATCCCACAA	40
	GCCGTCATGG ATATGGTGGC GGGGGCCAC TGGGGAGTCC	80
	TGGCGGGCCT TGCCTACTAT	100

25

(2) INFORMATION FOR SEQ ID NO: 27

SUBSTITUTE SHEET

- 76 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
10 (C) INDIVIDUAL ISOLATE: ARG2
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27
AGCAGCCCTA GTGGTGTGCG AGTTACTCCG GATCCCACAA 40
AGCATCGTGG ACATGGTGGC GGGGGCCAC TGGGGAGTCC 80
15 TGGCGGGCCT TGCTTACTAT 100
- (2) INFORMATION FOR SEQ ID NO: 28
- (i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 77 -

(C) INDIVIDUAL ISOLATE: I15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28

5 GGCAGCCCTA GTGGTGTGCG AGTTACTCCG GATCCCGCAA 40
GCTGTCGTGG ACATGGTGGC GGGGGCCCCAC TGGGGAATCC 80
TAGCGGGTCT TGCCTACTAT 100

(2) INFORMATION FOR SEQ ID NO: 29

10 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 100 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: GH8

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29

TGTGGGTATG GTGGTGGCGC ACGTCCTGCG TTTGCCCCAG 40
ACCTTGTTTCG ACATAATAGC CGGGGCCCCAT TGGGGCATCT 80
TGGCGGGCTT GGCCTATTAC 100

25

(2) INFORMATION FOR SEQ ID NO: 30

SUBSTITUTE SHEET

- 78 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 5
- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: I4
- 10
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30
TGTGGGTATG GTGGTAGCAC ACGTCCTGCG TCTGCCCCAG 40
ACCTTGTTTCG ACATAATAGC CGGGGCCCAT TGGGGCATCT 80
TGGCAGGCCT AGCCTATTAC 100
- 15
- (2) INFORMATION FOR SEQ ID NO: 31
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20
- (ii) MOLECULE TYPE: DNA
- 25
- (vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 79 -

(C) INDIVIDUAL ISOLATE: I11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31

5 TGTGGGTATG GTGGTGGCGC AAGTCCTGCG TTTGCCCCAG 40
ACCTTGTTTCG ACGTGCTAGC CGGGGCCCCAT TGGGGCATCT 80
TGGCGGGCCT GGCCTATTAC 100

(2) INFORMATION FOR SEQ ID NO: 32

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: I10

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32

TACCACTATG CTCCTGGCAT ACTTGGTGCG CATCCCGGAG 40
GTCATCCTGG ACATTATCAC GGGAGGACAC TGGGGCGTGA 80
TGTTTGGCCT GGCTTATTTC 100

25

(2) INFORMATION FOR SEQ ID NO: 33

SUBSTITUTE SHEET

- 80 -

(i). SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE: (ATCC # 40394)

10

(C) INDIVIDUAL ISOLATE: hcv1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC 120
GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCAAGACTG 160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC 200
TGCCTGATAG GGTGCTTGCG AGTGCCCCCG GAGGTCTCGT 240
AGACCGTGCA CC 252

15

20

(2) INFORMATION FOR SEQ ID NO: 34

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

SUBSTITUTE SHEET

- 81 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(c) INDIVIDUAL ISOLATE: us5

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34

GTTAGTATGA	GTGTCGTGCA	GCCTCCAGGA	CCCCCCTCC	40
CGGGAGAGCC	ATAGTGGTCT	GCGGAACCGG	TGAGTACACC	80
GGAATTGCCA	GGACGACCGG	GTCCTTTCTT	GGATCAACCC	120
GCTCAATGCC	TGGAGATTTG	GGCGTGCCCC	CGCAAGACTG	160
CTAGCCGAGT	AGTGTGGGT	CGCGAAAGGC	CTTGTGGTAC	200
TGCCTGATAG	GGTGCTTGCG	AGTGCCCCGG	GAGGTCTCGT	240
AGACCGTGCA	CC			252

15 (2) INFORMATION FOR SEQ ID NO: 35

(i) SEQUENCE CHARACTERISTICS:

(A)	LENGTH: 252 nucleotides
(B)	TYPE: nucleic acid
(C)	STRANDEDNESS: single
(D)	TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(c) INDIVIDUAL ISOLATE: aus1

SUBSTITUTE SHEET

- 82 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
5	GCTCAATGCC TGGAGATTG GGCACGCCCC CGCAAGATCA	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCCG GAGGTCTCGT	240
	AGACCGTGCA CC	252

10 (2) INFORMATION FOR SEQ ID NO: 36

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: sp2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
25	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATAAACCC	120
	GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160

SUBSTITUTE SHEET

- 83 -

CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

5 (2) INFORMATION FOR SEQ ID NO: 37

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gm2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
20 CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCAAGACTG	160
CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
25 AGACCGTGCA CC	252

(2) INFORMATION FOR SEQ ID NO: 38

SUBSTITUTE SHEET

- 84 -

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10

(C) INDIVIDUAL ISOLATE: i21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
15 GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATAAACCC 120
GCTCAATGCC TGGAGATTG GGCCTGCCCC CGCAAGACTG 160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC 200
TGCCTGATAG GGTGCTTGCG AGTGCCCCCG GAGGTCTCGT 240
AGACCGTGCA CC 252

20

(2) INFORMATION FOR SEQ ID NO: 39

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

SUBSTITUTE SHEET

- 85 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: us4

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39

GTTAGTATGA	GTGTCGTGCA	GCCTCCAGGA	CCCCCCTCC	40
CGGGAGAGCC	ATAGTGGTCT	GCGGAACCGG	TGAGTACACC	80
GGAATTGCCA	GGACGACCGG	GTCCTTTCTT	GGATCAACCC	120
GCTCAATGCC	TGGAGATTTG	GGCGTGCCCC	CGCGAGACTG	160
CTAGCCGAGT	AGTGTTGGGT	CGCGAAAGGC	CTTGTGGTAC	200
TGCCTGATAG	GGTGCTTGCG	AGTGCCCCCGG	GAGGTCTCGT	240
AGACCGTGCA	CC			252

15 (2) INFORMATION FOR SEQ ID NO: 40

(i) SEQUENCE CHARACTERISTICS:

(A)	LENGTH: 252 nucleotides
(B)	TYPE: nucleic acid
(C)	STRANDEDNESS: single
(D)	TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: jh1

SUBSTITUTE SHEET

- 86 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
5	GCTCAATGCC TGGAGATTG GCGTGCCCC CGCGAGACTG	160
	CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA TC	252

10 (2) INFORMATION FOR SEQ ID NO: 41

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: nac5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
25	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
	GCTCAATGCC TGGAGATTG GCGTGCCCC CGCGAGACTG	160

SUBSTITUTE SHEET

- 87 -

CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC 200
 TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
 AGACCGTGCA CC 252

5 (2) INFORMATION FOR SEQ ID NO: 42

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 15 (C) INDIVIDUAL ISOLATE: arg2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC 40
 CGGGAGAGCC ATAGTGGTCT GCGBAACCGG TGAGTACACC 80
 20 GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC 120
 GCTCAATGCC TGGAGATTTG GCGTGCCCC CGCGAGACTG 160
 CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC 200
 TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
 AGACCGTGCA CC 252

25

(2) INFORMATION FOR SEQ ID NO: 43

SUBSTITUTE SHEET

- 88 -

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10 (C) INDIVIDUAL ISOLATE: spl

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43

GTTAGTATGA	GTGTCGTGCA	GCCTCCAGGA	CCCCCCTCC	40
CGGGAGAGCC	ATAGTGGTCT	GCGGAACCGG	TGAGTACACC	80
15 GGAATTGCCA	GGACGACCGG	GTCCTTTCTT	GGATCAACCC	120
GCTCAATGCC	TGGAGATTTG	GGCGTGCCCC	CGCGAGACTG	160
CTAGCCGAGT	AGTGTTGGGT	CGCGAAAGGC	CTTGTGGTAC	200
TGCCTGATAG	GGTGCTTGCG	AGTGCCCCCG	GAGGTCTCGT	240
20 AGACCGTGCA	CC			252

(2) INFORMATION FOR SEQ ID NO: 44

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

25 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 89 -

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ghi

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160
CTAGCCGAGT AGTGTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

10

15 (2) INFORMATION FOR SEQ ID NO: 45

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: i15

SUBSTITUTE SHEET

- 90 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
5	GCTCAATGCC TGGAGATTG GGC GTGCCCC CGCGAGACTG	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA CC	252

10 (2) INFORMATION FOR SEQ ID NO: 46

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

(C)	INDIVIDUAL ISOLATE: i10
-----	-------------------------

SUBSTITUTE SHEET

- 91 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46

GCTAGTATCA GTGTCGTACA GCCTCCAGGC CCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCG GGAAGACTGG GTCCTTTCTT GGATAAACCC	120
ACTCTATGCC CGGCCATTG GGCCTGCCCC CGCAAGACTG	160
CTAGCCGAGT AGCGTTGGGT TCGGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA TC	252

10 (2) INFORMATION FOR SEQ ID NO: 47

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: arg6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47

GTTAGTATGA GTCTCGTACA GCCTCCAGGC CCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCTG GGAAGACTGG GTCCTTTCTT GGATAAACCC	120
ACTCTATGCC CAGCCATTG GGCCTGCCCC CGCAAGACTG	160

SUBSTITUTE SHEET

- 92 -

CTAGCCGAGT AGCGTTGGGT TCGAAAGGC CTTGTGGTAC 200
 TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
 AGACCGTGCA TC 252

5 (2) INFORMATION FOR SEQ ID NO: 48

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 15 (C) INDIVIDUAL ISOLATE: s21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48

20 GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CTCCCCCTCC 40
 CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
 GGAATCGCTG GGGTGACCGG GTCCTTTCTT GGAGCAACCC 120
 GCTCAATACC CAGAAATTG GCGGTGCCCC CGCGAGATCA 160
 CTAGCCGAGT AGTGTGCGGT CGCGAAAGGC CTTGTGGTAC 200
 TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
 25 AGACCGTGCA AC 252

(2) INFORMATION FOR SEQ ID NO: 49

SUBSTITUTE SHEET

- 93 -

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10 (vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: gj61329

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49

15	GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATCGCTG GGGTGACCGG GTCCTTTCTT GGAGTAACCC	120
	GCTCAATACC CAGAAATTTG GGC GTGCCCC CGCGAGATCA	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
20	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA AC	252

(2) INFORMATION FOR SEQ ID NO: 50

25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 180 nucleotides

SUBSTITUTE SHEET

- 94 -

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: DNA
(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: sa3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50

10

GTTAGTATGA	GTGTCGAACA	GCCTCCAGGA	CCCCCCTCC	40
CGGGAGAGCC	ATAGTGGTCT	GCGGAACCGG	TGAGTACACC	80
GGAATTGCCG	GGATGACCGG	GTCCTTTCTT	GGATAAACCC	120
GCTCAATGCC	CGGAGATTTG	GGCGTGCCCC	CGCGAGACTG	160
CTAGCCGAGT	AGTGTTGGGT			180

15

(2) INFORMATION FOR SEQ ID NO: 51

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 180 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20

25 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 95 -

(C) INDIVIDUAL ISOLATE: sa4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51

5 GTTAGTATGA GTGTCGAACA GCCTCCAGGA CCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80

GGAATTGCCG GGATGACCGG GTCCTTTCTT GGATAAACCC 120
GCTCAATGCC CGGAGATTG GCGTGCCCC CGCGAGACTG 160
CTAGCCGAGT AGTGTTGGGT 180

10

(2) INFORMATION FOR SEQ ID NO: 52

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE: (ATCC # 40394)

(C) INDIVIDUAL ISOLATE: hcv1

SUBSTITUTE SHEET

- 96 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52

	ATGAGCACGA ATCCTAAACC TCAAAAAAAAA AACAAACGTA	40
	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
5	GGCCCTAGAT TGGGTGTGCG CGCGACGAGA AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
	GGCTCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCCGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGC TCGGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
10	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT ACCGCTCGTC GGCGCCCCTC TTGGAGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGAAC ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
15	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 53

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

- 97 -

(C) INDIVIDUAL ISOLATE: us5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
5	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
	GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
10	TACCCCTGGC CCCTCTATGG CAATGAGGGT TGCGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGTTG	320
	GGGCCCCACA GACCCCGGC GTAGGTCGCG CAATTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCACA	400
	TGGGGTACAT ACCGCTCGTC GCGCCCCCTC TTGGAGGCGC	440
15	TGCCAGGGCT CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGAACT ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 54

20

(i) SEQUENCE CHARACTERISTICS:

- | | |
|----|-----------------------------|
| | (A) LENGTH: 549 nucleotides |
| | (B) TYPE: nucleic acid |
| | (C) STRANDEDNESS: single |
| 25 | (D) TOPOLOGY: linear |

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 98 -

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: aus1

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54
 ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG TCGCCACAG GACGTTAAGT TCCGGGTGG 80
 CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG 120
 GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG 160
 10 AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCTAA 200
 GGC GCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG 240
 TACCCCTGGC CCCTCTATGG TAATGAGGGT TGCGGATGGG 280
 CGGGATGGCT CCTGTCCCCC CGTGGCTCTC GGCCTAGTTG 320
 GGGCCCTACA GACCCCGGC GTAGGTCGCG CAATTGGGT 360
 15 AAGGTCATCG ATACCCTCAC GTGCGGCTTC GCCGACCACA 400
 TGGGGTACAT TCCGCTCGTT GGC GCGCCCTC TTGGGGGCGC 440
 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC 480
 GCGTGAACT ATGCAACAGG GAATCTTCCT GGTGCTCTT 520
 TCTCTATCTT CCTTCTGGCC CTTCTCTCT 549

20

(2) INFORMATION FOR SEQ ID NO: 55

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

25 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

SUBSTITUTE SHEET

- 99 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: sp2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
10	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CACGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CCATCCCCAA	200
	GGCTCGTCGA CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGC TCGGGGTGGG	280
15	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT ACCGCTCGTC GGCGCCCTC TTGGAGGCGC	440
	TGCCAGAGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
20	GGCGTGA ACT ATGCAACAGG GAACCTTCCC GGTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 56

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

SUBSTITUTE SHEET

- 100 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gm2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56

10	ATGAGCACGA ATCCTAAACC TCAAAGAAGA ACCAAACGTA	40
	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
15	GGCACGTCGG CCCGAGGGTA GGACCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGT TCGGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGCGGCTCTC GGCCTAACTG	320
	GGGCCCCACA GACCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
20	TGGGGTACAT ACCGCTCGTC GGCGCCCTC TTGGAGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGAAC ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

25 (2) INFORMATION FOR SEQ ID NO: 57

(i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 101 -

- (A) LENGTH: 549 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
 - (C) INDIVIDUAL ISOLATE: i21

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
AGCGGTCGCA ACCTCGTGGT AGACGCCAGC CTATCCCCAA	200
GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
TACCCTTGGC CCCTCTATGG CAATGAGGGT TCGGGGTGGG	280
CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT	360
AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
TGGGGTACAT ACCGCTCGTC GGCGCCCCTC TTGGAGGCGC	440
TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
GGCGTGA ACT ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
TTTCTATTTT CCTTCTGGCC CTGCTCTCT	549

15

20

25

- (2) INFORMATION FOR SEQ ID NO: 58

SUBSTITUTE SHEET

- 102 -

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10 (C) INDIVIDUAL ISOLATE: us4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
	ACACCAACCG CCGCCCACAG GACGTTAAGT TCCCGGGCGG	80
15	TGGCCAGGTC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG	120
	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
	GGCTCGCCAG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG	280
20	CAGGATGGCT CCTGTCACCC CGTGGCTCTC GGCCTAGTTG	320
	GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTTGGGT	360
	AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT TCCGCTCGTC GGCGCCCCCC TTAGGGGCGC	440
	TGCCAGGGCC TTGGCGCATG GCGTCCGGGT TCTGGAGGAC	480
25	GGCGTGAACT ACGCAACAGG GAATCTGCCC GGTGCTCCT	520
	TTTCTATCTT CCTCTTGGCT CTGCTGTCC	549

SUBSTITUTE SHEET

- 103 -

(2) INFORMATION FOR SEQ ID NO: 59

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: jh1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59

15 ATGAGCACAA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCACAG GACGTCAAGT TCCCGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120
 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
 AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
 20 GGCTCGCCAG CCGAGGGCA GGGCCTGGGC TCAGCCCGGG 240
 TACCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGCG 280
 CAGGATGGCT CCTGTACCC CGTGGCTCTC GGCCTAGTTG 320
 GGGCCCCACG GACCCCGGC GTAGGTCGCG TAATTGGGT 360
 AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA 400
 25 TGGGGTACAT TCCGCTTGTC GCGCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAGGAC 480
 GGCGTGA ACT ATGCAACAGG GAATTGCCC GGTGCTCTT 520

SUBSTITUTE SHEET

- 104 -

TCTCTATCTT CCTCTTGGCT CTGCTGTCC

549

(2) INFORMATION FOR SEQ ID NO: 60

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: nac5

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60
ATGAGCACAA ATCCTAAACC CCAAAGAAAA ACCAAACGTA 40
ACACCAACCG TCGCCCACAG GACGTCAAGT TCCCGGGCGG 80
TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120
20 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
GGCTCGCCGG CCCGAGGGCA GGTCTTGGGC TCAGCCCGGG 240
TACCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGGG 280
CAGGATGGCT CCTGTACCC CGCGGCTCCC GGCCTAGTTG 320
25 GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTTGGGT 360
AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA 400

SUBSTITUTE SHEET

- 105 -

TGGGGTACAT TCCGCTCGTC GCGCCCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAGGAC 480
 GCGGTGAACT ATGCAACAGG GAATTGCTCTT 520
 TCTCTATCTT CCTCTTGGCT CTGCTGTCC 549

5

(2) INFORMATION FOR SEQ ID NO: 61

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

15

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: arg2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCCACAG GACGTCAAGT TCCCGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG 120
 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
 AGCGGTGCGA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
 GGCTCGCCAG CCCGAGGGTA GGGCCTGGGC TCAGCCCGGG 240
 TACCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG 280
 CAGGGTGGCT CCTGTCCCCC CGCGGCTCCC GGCCTAGTTG 320

20

25

SUBSTITUTE SHEET

- 106 -

GGGCCCCACA GACCCCCGGC GTAGGTCGCG TAATTTGGGT 360
 AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA 400
 TGGGGTACAT TCCGCTCGTC GGC GCCCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC 480
 5 GCGTGAACT ATGCAACAGG GAATCTGCCC GGTGCTCTT 520
 TCTCTATCTT CCTCTTGGCT TTGCTGTCC 549

(2) INFORMATION FOR SEQ ID NO: 62

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: spl

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCCACAG GACGTCAAGT TCCCGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120
 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
 25 AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
 GGCTCGCCGG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG 240
 TATCCTTGGC CCCTCTATGG CAATGAGGGT CTGGGGTGGG 280

SUBSTITUTE SHEET

- 107 -

CAGGATGGCT CCTGTCACCC CGCGGCTCTC GGCCTAGCTG 320
 GGGCCCTACC GACCCCCGGC GTAGGTCGCG CAACTTGGGT 360
 AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA 400
 TGGGGTACAT TCCGCTCGTC GGC GCCCCCCC TTAGGGGCGC 440
 5 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC 480
 GCGGTGAACT ATGCAACAGG GAATTTGCCC GGTGCTCTT 520
 TCTCTATCTT CCTCTTGGCT TTGCTGTCC 549

(2) INFORMATION FOR SEQ ID NO: 63

10

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

20

(C) INDIVIDUAL ISOLATE: gh1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCACAG GACGTCAAGT TCCCGGGCGG 80
 25 TGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG 120
 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
 AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200

SUBSTITUTE SHEET

- 108 -

5 GGCTCGCCGG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG 240
 TACCCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG 280
 CAGGATGGCT CCTGTCACCC CGTGGTTCTC GGCCTAGTTG 320
 GGGCCCCACG GACCCCCGGC GTAGGTCGCG CAATTTGGGT 360
 AAGATCATCG ATACCCTCAC GTGCGGCTTC GCCGACCTCA 400
 TGGGGTACAT TCCGCTCGTC GGC GCCCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC 480
 GGC GTGA ACT ATGCAACAGG GAATCTGCCC GGTTGCTCCT 520
 TTTCTATCTT CCTTCTGGCT TTGCTGTCC 549

10

(2) INFORMATION FOR SEQ ID NO: 64

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: i15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64

25 ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCACAG GACGTCAAGT TCCGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120

SUBSTITUTE SHEET

- 109 -

	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
	AGCGGTTCGA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
	GGCTCGCCAG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG	240
	TACCCCTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG	280
5	CAGGATGGCT CCTGTACCCC CGCGGCTCCC GGCCTAGTTG	320
	GGGCCCCAAA GACCCCCGGC GTAGGTGCGG TAATTTGGGT	360
	AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT TCCGCTCGTC GGC GCCCCCT TAGGGGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC	480
10	GGCGTGAAC ATGCAACAGG GAATCTACCC GGTGCTCTT	520
	TCTCTATCTT CCTCTTGGCT TTGCTGTCC	549

(2) INFORMATION FOR SEQ ID NO: 65

15 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: 110

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65

ATGAGCACAA ATCCTAAACC TCAAAGAAAA ACCAAAAGAA 40

SUBSTITUTE SHEET

- 110 -

	ACACTAACCG	CCGCCCACAG	GACGTCAAGT	TCCCGGGCGG	80
	TGGCCAGATC	GTTGGCGGAG	TATACTTGCT	GCCGCGCAGG	120
	GGCCCGAGAT	TGGGTGTGCG	CGCGACGAGG	AAAACCTCCG	160
	AACGATCCCA	GCCACGCGGA	AGGCGTCAGC	CCATCCCTAA	200
5	AGATCGTCGC	ACCGCTGGCA	AGTCCTGGGG	AAGGCCAGGA	240
	TATCCTTGGC	CCCTGTATGG	GAATGAGGGT	CTCGGCTGGG	280
	CAGGGTGGCT	CCTGTCCCCC	CGTGGCTCTC	GCCCTTCATG	320
	GGGCCCCACT	GACCCCCGGC	ATAGATCGCG	CAACTTGGGT	360
	AAGGTCATCG	ATACCCTAAC	GTGCGGTTTT	GCCGACCTCA	400
10	TGGGGTACAT	TCCCGTCATC	GGCGCCCCCG	TTGGAGGCGT	440
	TGCCAGAGCT	CTCGCCCACG	GAGTGAGGGT	TCTGGAGGAT	480
	GGGGTAAATT	ATGCAACAGG	GAATTTGCCC	GGTTGCTCTT	520
	TCTCTATCTT	TCTCTTAGCC	CTCTTGTCT		549

15 (2) INFORMATION FOR SEQ ID NO: 66

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 510 nucleotides
 (B) TYPE: nucleic acid
 20 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: arg6

SUBSTITUTE SHEET

- 111 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66

	ATGAGCACAA ATCCTCAACC TCAAAGAAAA ACCAAAAGAA	40
	ACACTAACCG CCGCCCACAG GACGTCAAGT TCCCGGGCGG	80
	TGGTCAGATC GTTGGCGGAG TATACTTGTT GCCGCGCAGG	120
5	GGCCCCAGGT TGGGTGTGCG CGCGACGAGG AAAACTTCCG	160
	AACGGTCCCA GCCACGTGGG AGGCGCCAGC CCATCCCCAA	200
	AGATCGGCGC ACCACTGGCA AGTCCTGGGG GAAGCCAGGA	240
	TACCCTTGGC CCCTGTATGG GAATGAGGGT CTCGGCTGGG	280
	CAGGGTGGCT CCTGTCCCCC CGCGGTTCTC GCCCTTCATG	320
10	GGGCCCCACT GACCCCCGGC ATAGATCACG CAACTTGGGT	360
	AAGGTCATCG ATACCCTAAC GTGTGGTTTT GCCGACCTCA	400
	TGGGGTACAT TCCCGTCGGT GGTGCCCCCG TTGGTGGTGT	440
	CGCCAGAGCC CTTGCCCATG GGGTGAGGGT TCTGGAAGAC	480
	GGGATAAATT ATGCAACAGG GAATCTGCCC	510

15

(2) INFORMATION FOR SEQ ID NO: 67

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 29 nucleotides
20	(B) TYPE: nucleic acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67

CAAACGTAAC ACCAACCGRC GCCCACAGG

29

SUBSTITUTE SHEET

- 112 -

(2) INFORMATION FOR SEQ ID NO: 68

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 24 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68
ACAGAYCCGC AKAGRTCCCC CACG

24

15 (2) INFORMATION FOR SEQ ID NO: 69

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 30 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69
CGAACCTCGA GGTAGACGTC AGCCTATCCC

30

SUBSTITUTE SHEET

- 113 -

(2) INFORMATION FOR SEQ ID NO: 70

(i) SEQUENCE CHARACTERISTICS:

5

- (A) LENGTH: 30 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70
GCAACCTCGT GGAAGGCGAC AACCTATCCC

30

(2) INFORMATION FOR SEQ ID NO: 71

15

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 30 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71
GTCACCAATG ATTGCCCTAA CTCGAGTATT

25

30

(2) INFORMATION FOR SEQ ID NO: 72

SUBSTITUTE SHEET

- 114 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72
GTCACGAACG ACTGCTCCAA CTCAAG 26
- (2) INFORMATION FOR SEQ ID NO: 73
- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73
TGGACATGAT CGCTGGWGCY CACTGGGG 28
- 25 (2) INFORMATION FOR SEQ ID NO: 74

SUBSTITUTE SHEET

- 115 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74
TGGAYATGGT GGYGGGGGCY CACTGGGG 28
- (2) INFORMATION FOR SEQ ID NO: 75
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75
ATGATGAACT GGTCVCCYAC 20
- (2) INFORMATION FOR SEQ ID NO: 76
- (i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 116 -

- (A) LENGTH: 26 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76

ACCTTVGCCC AGTTSCCCRC CATGGA

26

10 (2) INFORMATION FOR SEQ ID NO: 77

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77

AACCCACTCT ATGYCCGGYC AT

22

(2) INFORMATION FOR SEQ ID NO: 78

25 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 nucleotides
- (B) TYPE: nucleic acid

SUBSTITUTE SHEET

- 117 -

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78
GAATCGCTGG GGTGACCG

18

(2) INFORMATION FOR SEQ ID NO: 79

10

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75
CCATGAATCA CTCCCCTGTG AGGA ACTA

20

28

(2) INFORMATION FOR SEQ ID NO: 80

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

25

SUBSTITUTE SHEET

- 118 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80

TTGCGGGGGC ACGCCCAA

18

(2) INFORMATION FOR SEQ ID NO: 81

(i) SEQUENCE CHARACTERISTICS:

10

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81

YGAAGCGGGC ACAGTCARRC AAGARAGCAG GGC

33

20

(2) INFORMATION FOR SEQ ID NO: 82

(i) SEQUENCE CHARACTERISTICS:

25

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

SUBSTITUTE SHEET

- 119 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82
RTARAGCCCY GWGGAGTTGC GCACTTGGTR GGC 33

(2) INFORMATION FOR SEQ ID NO: 83

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83
RATACTCGAG TTAGGGCAAT CATTGGTGAC RTG 33

20 (2) INFORMATION FOR SEQ ID NO: 84

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 120 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84

AGYRTGCAGG ATGGYATCRK BCGYCTCGTA CAC 33

5

(2) INFORMATION FOR SEQ ID NO: 85

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85

GTTRCCCTCR CGAACGCAAG GGACRCACCC CGG 33

(2) INFORMATION FOR SEQ ID NO: 86

20 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 121 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86
CGTRGGGGTY AYC GCCACCC AACACCTCGA GRC

33

(2) INFORMATION FOR SEQ ID NO: 87

5

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87
CGTYGYGGGG AGTTTGCCRT CCCTGGTGGC YAC

15

33

(2) INFORMATION FOR SEQ ID NO: 88

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88

SUBSTITUTE SHEET

- 122 -

CCCGACAAGC AGATCGATGT GACGTCGAAG CTG

33

(2) INFORMATION FOR SEQ ID NO: 89

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89

CCCCACGTAG ARGGCCGARC AGAGRGTGGC GCY

33

15

(2) INFORMATION FOR SEQ ID NO: 90

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

20

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90

YTGRCCGACA AGAAAGACAG ACCCGCAYAR GTC

33

SUBSTITUTE SHEET

- 123 -

(2) INFORMATION FOR SEQ ID NO: 91

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91
CGTCCAGTGG YGCCTGGGAG AGAAGGTGAA CAG

33

15 (2) INFORMATION FOR SEQ ID NO: 92

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92
GCCGGGATAG ATRGARCAAT TGCARYCTTG CGT

33

SUBSTITUTE SHEET

- 124 -

(2) INFORMATION FOR SEQ ID NO: 93

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93

CATATCCCAT GCCATGCGGT GACCCGTTAY ATG 33

(2) INFORMATION FOR SEQ ID NO: 94

15

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94

25 YACCAAYGCC GTCGTAGGGG ACCARTTCAT CAT 33

(2) INFORMATION FOR SEQ ID NO: 95

SUBSTITUTE SHEET

- 125 -

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 33 nucleotides
 (B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95
10 GATGGCTTGT GGGATCCGGA GYASCTGAGC YAY 33
- (2) INFORMATION FOR SEQ ID NO: 96
- (i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 33 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96
GACTCCCCAG TGRGCWCCAG CGATCATRTC CAW 33
- 25 (2) INFORMATION FOR SEQ ID NO: 97
- (i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 126 -

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97
CCCCACCATG GAGAAATACG CTATGCCCGC YAG 33

10 (2) INFORMATION FOR SEQ ID NO: 98

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

- (ii) MOLECULE TYPE: DNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98
TAGYAGCAGY ACTACYARGA CCTTCGCCCA GTT 33

(2) INFORMATION FOR SEQ ID NO: 99

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid

25

SUBSTITUTE SHEET

- 127 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99

GSTGACGTGR GTKTCYGCGT CRACGCCGGC RAA

33

(2) INFORMATION FOR SEQ ID NO: 100

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100

20

GGAAGYTGGG ATGGTYARRC ARGASAGCAR AGC

33

(2) INFORMATION FOR SEQ ID NO: 101

(i) SEQUENCE CHARACTERISTICS:

25

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

SUBSTITUTE SHEET

- 128 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101
GTAYAYYCCG GACRCGTTGC GCACTTCRTA AGC 33
(2) INFORMATION FOR SEQ ID NO: 102

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102
AATRCCTTGMG TTGGAGCART CGTTYGTGAC ATG 33

20 (2) INFORMATION FOR SEQ ID NO: 103

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 129 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103
RGYRTGCATG ATCAYGTCCG YGCCTCATA CAC

33

5

(2) INFORMATION FOR SEQ ID NO: 104

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104
RTTGTYTCC CGRACGCARG GCACGCACCC RGG

33

(2) INFORMATION FOR SEQ ID NO: 105

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 130 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105
CGTGGGGRGTS AGCGCYACCC AGCARCGGGA GSW 33

(2) INFORMATION FOR SEQ ID NO: 106

5

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106
15 YGTRGTGGGG AYGCTGKHRT TCCTGGCCGC VAR 33

(2) INFORMATION FOR SEQ ID NO: 107

(i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107

SUBSTITUTE SHEET

- 131 -

CCCRACGAGC AARTCGACRT GRCGTCGTAW TGT

33

(2) INFORMATION FOR SEQ ID NO: 108

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108
YCCCACGTAC ATAGCSGAMS AGARRGYAGC CGY

33

15

(2) INFORMATION FOR SEQ ID NO: 109

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109
CTGGGAGAYR AGRAAAACAG ATCCGCARAG RTC

33

SUBSTITUTE SHEET

- 132 -

(2) INFORMATION FOR SEQ ID NO: 110

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110

YGTCTCRTGC CGGCCAGSBG AGAAGGTGAA YAG 33

15 (2) INFORMATION FOR SEQ ID NO: 111

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111

GCCGGGATAG AKKGAGCART TGCAKTCCTG YAC 33

SUBSTITUTE SHEET

- 133 -

(2) INFORMATION FOR SEQ ID NO: 112

(i) SEQUENCE CHARACTERISTICS:

5

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112

CATATCCCAA GCCATRCGRT GGCCTGAYAC CTG

33

(2) INFORMATION FOR SEQ ID NO: 113

15

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113

25

CACTARGGCT GYGTRGGYG ACCAGTTCAT CAT

33

(2) INFORMATION FOR SEQ ID NO: 114

SUBSTITUTE SHEET

- 134 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114
10 GACRGCTTGT GGGATCCGGA GTAACGCGA YAC 33
- (2) INFORMATION FOR SEQ ID NO: 115
- (i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115
GACTCCCCAG TGRGCCCCCG CCACCATRTC CAT 33
- 25 (2) INFORMATION FOR SEQ ID NO: 116
- (i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 135 -

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116
SCCCACCATG GAWWAGTAGG CAAGGCCCGC YAG 33

10 (2) INFORMATION FOR SEQ ID NO: 117

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117
GAGTAGCATC ACAATCAADA CCTTAGCCCA GTT 33

(2) INFORMATION FOR SEQ ID NO: 118

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid

SUBSTITUTE SHEET

- 136 -

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118
YGWCRYGYRG GTRTKCCCGT CAACGCCGGC AAA

33

(2) INFORMATION FOR SEQ ID NO: 119

10

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119
TCCTCACAGG GGAGTGATTC ATGGTGGAGT GTC

20

33

(2) INFORMATION FOR SEQ ID NO: 120

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

25

SUBSTITUTE SHEET

- 137 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120
ATGGCTAGAC GCTTTCTGCG TGAAGACAGT AGT 33
(2) INFORMATION FOR SEQ ID NO: 121

(i) SEQUENCE CHARACTERISTICS:
10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121
GCCTGGAGGC TGCACGRCAC TCATACTAAC GCC 33

20 (2) INFORMATION FOR SEQ ID NO: 122

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
25 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 138 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122
CGCAGACCAC TATGGCTCTY CCGGGAGGGG GGG

33

5

(2) INFORMATION FOR SEQ ID NO: 123

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123
TCRTCCYGGC AATTCCGGTG TACTCACCGG TTC

33

(2) INFORMATION FOR SEQ ID NO: 124

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 139 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124
GCATIGAGCG GGTTCATCCA AGAAAGGACC CGG 33

(2) INFORMATION FOR SEQ ID NO: 125

5

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125
AGCAGTCTYG CGGGGGCAGC CCCAARTCTC CAG 33

15

(2) INFORMATION FOR SEQ ID NO: 126

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126

SUBSTITUTE SHEET

- 140 -

ACAAGGCCTT TCGCGACCCA ACACTACTCG GCT

33

(2) INFORMATION FOR SEQ ID NO: 127

- 5 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

10

- (ii) MOLECULE TYPE: DNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127

GGGGCACTCG CAAGCACCT ATCAGGCAGT ACC

33

15

(2) INFORMATION FOR SEQ ID NO: 128

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 141 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128

5 YGTGCTCATG RTGCACGGTC TACGAGACCT CCC 33

(2) INFORMATION FOR SEQ ID NO: 129

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129

GTTACGTTTG KTTYTTYTTT GRGGTTTRGG AWT 33

20 (2) INFORMATION FOR SEQ ID NO: 130

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 142 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130

CGGGAACTTR ACGTCCTGTG GGCGRCGGTT GGT 33

5

(2) INFORMATION FOR SEQ ID NO: 131

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

10 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131

CARGTAAACT CCACCRACGA TCTGRCCRCC RCC 33

(2) INFORMATION FOR SEQ ID NO: 132

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

SUBSTITUTE SHEET

- 143 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132
RCGCACACCC AAYCTRGGGC CCCTGCGCGG CAA 33

5 (2) INFORMATION FOR SEQ ID NO: 133

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
10 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133
15 AGGTTGCGAC CGCTCGGAAG TCTTYCTRGT CGC 33

(2) INFORMATION FOR SEQ ID NO: 134

(i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134

SUBSTITUTE SHEET

- 144 -

RCGHRCCTTG GGGATAGGCT GACGTCWACC TCG

33

(2) INFORMATION FOR SEQ ID NO: 135

5 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135

RCGHRCCTTG GGGATAGGTT GTCGCCWTCC ACG

33

15 (2) INFORMATION FOR SEQ ID NO: 136

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136

YCCRGGCTGR GCCCAGRYCC TRCCCTCGGR YYG

33

SUBSTITUTE SHEET

- 145 -

(2) INFORMATION FOR SEQ ID NO: 137

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137
BSHRCCCTCR TTRCCRTAGA GGGGCCADGG RTA 33

(2) INFORMATION FOR SEQ ID NO: 138

15

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138
GCCRCGGGGW GACAGGAGCC ATCCYGCCCA CCC 33

(2) INFORMATION FOR SEQ ID NO: 139

SUBSTITUTE SHEET

- 146 -

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139
CCGGGGGTCY GTGGGGCCCC AYCTAGGCCG RGA 33
- (2) INFORMATION FOR SEQ ID NO: 140
- (i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140
ATCGATGACC TTACCCAART TRCGCGACCT RCG 33
- 25 (2) INFORMATION FOR SEQ ID NO: 141
- (i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET

- 147 -

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141
CCCCATGAGR TCGGCGAAGC CGCAYGTRAG GGT

33

10

(2) INFORMATION FOR SEQ ID NO: 142

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142
GCCYCCWARR GGGGCGCCGA CGAGCGGWAT RTA

33

(2) INFORMATION FOR SEQ ID NO: 143

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid

SUBSTITUTE SHEET

- 148 -

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143

AACCCGGACR CCRTGYGCCA RGGCCCTGGC AGC 33

(2) INFORMATION FOR SEQ ID NO: 144

10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144

RTTCCCTGTT GCATAGTTCA CGCCGTCYTC CAG 33

20

(2) INFORMATION FOR SEQ ID NO: 145

25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

SUBSTITUTE SHEET

- 149 -

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145
5 CARRAGGAAG AKAGAGAAAG AGCAACCRGG MAR 33

(2) INFORMATION FOR SEQ ID NO: 146

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146
AGGCATAGGA CCCGTGTCTT 20

20 (2) INFORMATION FOR SEQ ID NO: 147

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147
CTTCTTTGGA GAAAGTGGTG 20

SUBSTITUTE SHEET

- 150 -

CLAIMS

1. As a composition of matter, a non-naturally occurring nucleic acid having a non-HCV-1 nucleotide
5 sequence of eight or more nucleotides corresponding to a nucleotide sequence within the hepatitis C virus genome.
2. The composition of claim 1 wherein said nucleotide
10 sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome is selected from the regions consisting of the NS5 region, envelope 1 region, 5'UT region, and the core region.
- 15 3. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the NS5 region.
- 20 4. The composition of claim 3 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome is selected from a sequence within sequences numbered 2-22.

SUBSTITUTE SHEET

- 151 -

5. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the envelope 1 region.

5

6. The composition of claim 5 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a sequence within sequence numbers 24-32.

10

7. The composition of claim 1 wherein at least one sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the 5'UT region.

15

8. The composition of claim 7 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a sequence within sequences numbered 34-51.

20

9. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the core region.

SUBSTITUTE SHEET

- 152 -

10. The composition of claim 9 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a within sequences numbered 53-66.

5

11. The composition of claim 1 wherein said non-naturally occurring nucleic acid has a nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

10

12. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences
15 numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, 33-38 in the 5'UT region, and 52-57 in the core region.

13. The composition of claim 11 wherein said
20 non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, 39-45 in the 5'UT region, and 58-64 in the
25 core region.

SUBSTITUTE SHEET

- 153 -

14. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences
5 numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

15. The composition of claim 11 wherein said
10 non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

15
16. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences
20 numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.

17. The composition of claim 1 wherein said
25 non-naturally occurring nucleic acid is capable of priming a reaction for the synthesis of nucleic acid to form a nucleic acid having a nucleotide sequence corresponding to hepatitis C virus.

SUBSTITUTE SHEET

- 154 -

18. The composition of claim 1 wherein said non-naturally occurring nucleic acid has label means for detecting a hybridization product.

5 19. The composition of claim 1 wherein said non-naturally occurring nucleic acid has support means for separating a hybridization product from solution.

20. The composition of claim 1 wherein said
10 non-naturally occurring nucleic acid prevents the transcription or translation of viral nucleic acid.

21. A method of forming a hybridization product with a hepatitis C virus nucleic acid comprising the following
15 steps:

a. placing a non-naturally occurring nucleic acid having a nucleotide sequence of eight or more nucleotides corresponding to a non-HCV-1 sequence in the hepatitis C viral genome into
20 conditions in which hybridization conditions can be imposed said non-naturally occurring nucleic acid capable of forming a hybridization product with said hepatitis C virus nucleic acid under hybridization
25 conditions; and

- 155 -

b. imposing hybridization conditions to form a hybridization product in the presence of hepatitis C virus nucleic acid.

5 22. The method of claim 21 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence in the hepatitis C virus genome corresponds to a sequence within at least one of the regions consisting essentially of NS5 region, envelope 1 region, 5'UT
10 region, and the core region.

23. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponds to a sequence within the NS5 region.
15

24. The method of claim 23 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponds to a sequence within sequences numbered 2-22.
20

25. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponds to a sequence within the envelope 1 region.

SUBSTITUTE SHEET

- 156 -

26. The method of claim 25 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence is selected from a sequence within sequences numbered 24-32.

5

27. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponding to a sequence within the 5'UT region.

10 28. The method of claim 27 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence selected from a sequence within sequences numbered 34-51.

15 29. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponding to a sequence within the core region.

20 30. The method of claim 29 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence selected from a sequence within sequences numbered 53-66.

25 31. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

SUBSTITUTE SHEET

- 157 -

32. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, 33-38 in the 5'UT region, and 52-57 in the core region.

33. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, 39-45 in the 5'UT region, and 58-64 in the core region.

34. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

35. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

SUBSTITUTE SHEET

- 158 -

36. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.
37. The method of claim 21 wherein said hybridization product is capable of priming a reaction for the synthesis of nucleic acid.
38. The method of claim 21 wherein said non-naturally occurring nucleic acid has label means for detecting a hybridization product.
39. The method of claim 21 wherein said non-naturally occurring nucleic acid has support means for separating the hybridization product from solution.
40. The method of claim 21 wherein said non-naturally occurring nucleic acid prevents the transcription or translation of viral nucleic acid.
41. As a composition of matter, a non-naturally occurring polypeptide corresponding to a non-HCV-1 nucleotide sequence of nine or more nucleotides which sequence of nine or more nucleotides corresponds to a sequence within hepatitis C virus genomic sequences.

- 159 -

42. The composition of claim 41 wherein said non-HCV-1 sequence is selected from one of the regions consisting of NS5 region, envelope 1 region, and the core region.
- 5 43. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence corresponds to a sequence in the NS5 region.
- 10 44. The composition of claim 43 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 2-22.
- 15 45. The composition of claim 41 wherein said non-HCV-1 sequence corresponds to a sequence in the envelope 1 region.
- 20 46. The composition of claim 45 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 24-32.
- 25 47. The composition of claim 41 wherein said non-HCV-1 sequence corresponds to a sequence in the core region.
48. The composition of claim 47 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 52-66.

SUBSTITUTE SHEET

- 160 -

49. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

5

50. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, and 52-57 in the core region.

51. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, and 58-64 in the core region.

52. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, and 65-66 in the core region.

SUBSTITUTE SHEET

- 161 -

53. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

54. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.

55. The composition of claim 41 wherein said polypeptide is capable of generating an immune reaction in a host.

56. An antibody capable of selectively binding to the composition of claim 41.

20

57. A method of detecting one or more genotypes of hepatitis C virus comprising the following steps:

a) placing a non-naturally occurring nucleic acid having a nucleotide sequence of eight or more nucleotides corresponding to one or more genotypes of hepatitis C virus under conditions where hybridization conditions can be imposed,

25

- 162 -

b) imposing hybridization conditions to form a hybridization product in the presence of hepatitis C virus nucleic acid; and

5 c) monitoring the non-naturally occurring nucleic acid for the formation of a hybridization product, which hybridization product is indicative of the presence of the genotype of hepatitis C virus.

10 58. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, 33-38 in the 5'UT region, and 52-57 in the core region.

15 59. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in
20 the NS5 region, 26-28 in the envelope 1 region, 39-45 in the 5'UT region, and 58-64 in the core region.

SUBSTITUTE SHEET

- 163 -

60. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

61. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

62. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region.

63. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 67-145.

SUBSTITUTE SHEET

- 164 -

64. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 69, 71, 73 and 81-99 to identify Group I genotypes in the core and region of the HCV genome.

65. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 70, 72, 70 and 100-118 to identify Group II genotypes in the core and envelope regions of the HCV genome.

66. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 77 to identify Group III genotypes in the 5' UT region of the HCV genome.

67. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence numbered 79 to identify Group IV genotypes in the 5' UT region of the HCV genome.

SUBSTITUTE SHEET

1/21

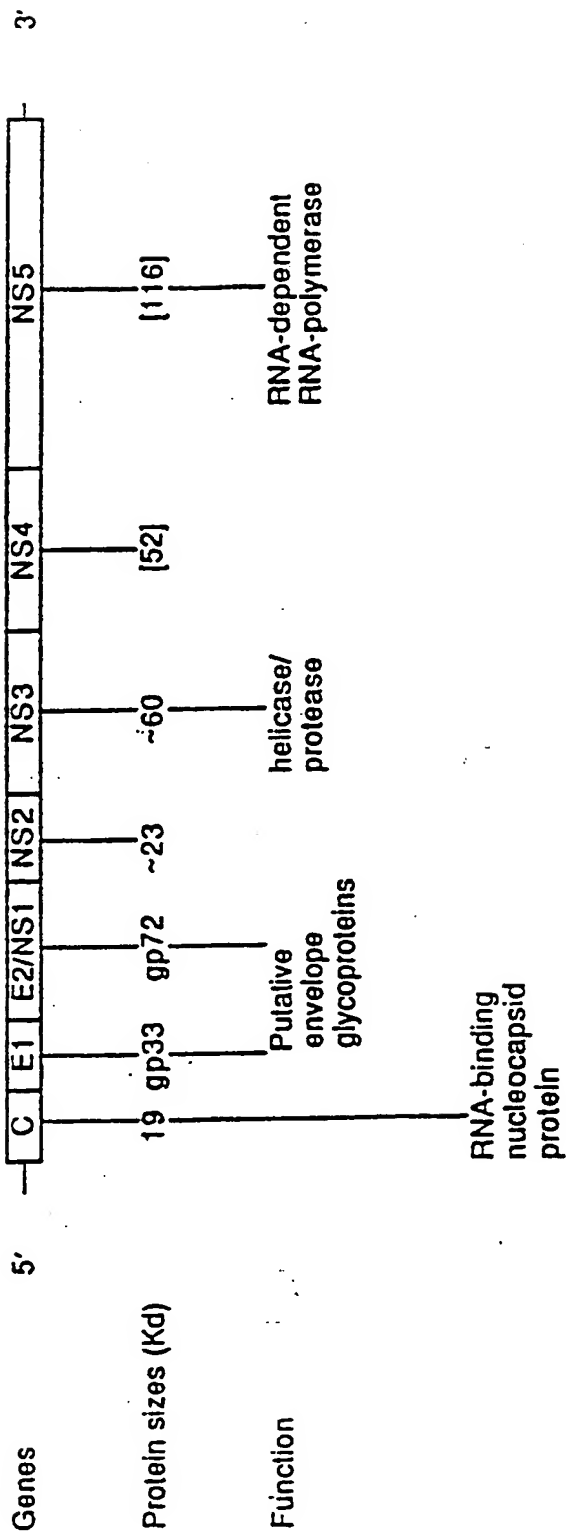


Fig. 1

2/21

Fig. 2a

NS5 REGION

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
=====	=====	=====	=====
1	GI	1	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT CGACCCCCAA
2		1	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATTTACCAAT GTTGTGACCT GGACCCCCAA
3		1	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGATCT GGACCCCCAA
4		1	CTCTACAGTC ACTGAGAAGC ACATCCGTAC GGAGGAGGCA ATTTACCAAT GTTGTGACCT GGACCCCCAA
5		1	CTCCACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT GGACCCCCAA
6		1	CTCTACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT GGACCCCCAA
=====	=====	=====	=====
7	GII	1	CTCCACAGTC ACTGAGAATG ACATCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACCT GGCCCCCGAA
8		1	CTCAACGGTC ACTGAGAATG ACATCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACCT GGCCCCCGAG
9		1	CTCAACGGTC ACCGAGAATG ACATCCGTGT TGAGGAGTCA ATTTATCAAT GTTGTGACCT GGCCCCCGAG
10		1	CTCAACGGTC ACTGAGAGTG ACATCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACCT GGCCCCCGAA
11		1	CTCCACAGTC ACTGAGAGTG ACATCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACCT GGCCCCCGAA
12		1	CTCAACAGTC ACTGAGAGTG ACATCCGTGT TGAGGAGTCA ATCTACCAAT GTTGTGACCT GGCCCCCGAA
=====	=====	=====	=====
13	GIII	1	CTCAACCGTC ACTGAGAGG ACATCAGAAC TGAGGAGTCC ATATACCGAG CTTGCTCCCT GCCTGAGGAG
14		1	CTCTACAGTC ACGTAAAGG ACATCAGATC CTAGGAGTCC ATCTACCAAT CTTGTTCACT GCCCGAGGAG
15		1	CTCTACAGTC ACAGAGAGGG ACATCAGAAC CGAGGAGTCC ATCTATCTGT CTTGCTCACT GCCTGAGGAG
16		1	CTCTACAGTC ACGGAGAGGG ACATCAGAAC CGAGGAGTCC ATCTATCTGT CTTGTTCACT GCCTGAGGAG
17		1	CTCAACCGTC ACGGAGAGGG ACATAAGAAC AGAAGAATCC ATATATCAGG GTTGTTCCT GCCTCAGGAG
=====	=====	=====	=====
18	GV	1	CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCT ATTTACCAAT CATTTACTTT GCAGCCTGAG
19		1	CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCC ATTTACCAAT CATTTACTTT GCAGCCTGAG
=====	=====	=====	=====
20	GIV	1	CTCTACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG
21		1	CTCGACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG
22		1	CTCAACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG
=====	=====	=====	=====

SUBSTITUTE SHEET

3/21

Fig. 2b

NS5 REGION - (2/5)

SEQUENCE			+++++		=====	
ID NUMBER	GENOTYPE					
1	GI	71	GCCCGCGTGG	CCATCAAGTC	CCTCACCGAG	AGGCTTTATG TTGGGGGCCC TCTTACCAAT TCAAGGGGGG
2	GI	71	GCCCGCATGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG TCGGGGGGCC TCTTACCAAT TCAAGGGGGG
3	GI	71	GCCCGCGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTACG TTGGGGGGCC TCTTACCAAT TCAAGGGGGG
4	GI	71	GCCCGCGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG TTGGGGGGCC CTTTACCAAT TCAAGGGGGG
5	GI	71	GCCCGCGTGG	CCATCAAGTC	CCTCACCGAG	AGGCTTTATG TCGGGGGGCC TCTTACCAAT TCAAGGGGGG
6	GI	71	GCCCGTGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG TTGGGGGGCC TCTTACCAAT TCAAGGGGGG
=====						
7	GII	71	GCCAGACAGG	CCATAAGGTC	GCTCACAGAG	CGGCTCTATG TCGGGGGTCC TATGACTAAC TCCAAAGGGC
8		71	GCCAGACAAG	CCATAAGGTC	GCTCACAGAG	CGGCTTTACA TCGGGGGGCC CCTGACTAAT TCAAAAGGGC
9		71	GCTAGACAGG	CCATAAGGTC	GCTCACAGAG	CGGCTTTATA TCGGGGGGCC CCTGACCAAT TCAAAAGGGC
10		71	GCCAGGCAGG	CCATAAGGTC	GCTCACCGAG	CGGCTTTATA TCGGGGGGCC CCTGACTAAT TCAAAAGGGC
11		71	GCCAGACAGG	CTATAAGGTC	GCTCACAGAG	CGGCTGTACA TCGGGGGTCC CCTGACTAAT TCAAAAGGGC
12		71	GCCAGACAGG	CTATAAGGTC	GCTCACAGAG	CGGCTTTACA TCGGGGGTCC CCTGACTAAT TCAAAAGGGC
=====						
13	GIII	71	GCTCACATTG	CCATACACTC	GCTGACTGAG	AGGCTCTACG TGGGAGGGCC CATGTTCAAC AGCAAGGGCC
14		71	GCTCGAACTG	CTATACACTC	ACTGACTGAG	AGACTATACG TAGGGGGGCC CATGACAAAC AGCAAGGGCC
15		71	GCCCGAACTG	CTATACACTC	ACTGACTGAG	AGACTGTACG TAGGGGGGCC CATGACAAAC AGCAAGGGCC
16		71	GCTCGAACTG	CCATACACTC	ACTGACTGAG	AGGCTGTACG TAGGGGGGCC CATGACAAAC AGCAAGGGCC
17		71	GCTAGAACTG	CTATCCACTC	GCTCACTGAG	AGACTCTACG TAGGAGGGCC CATGACAAAC AGCAAGGGAC
=====						
18	GV	71	GCGCGTGTGG	CAATACGGTC	ACTCACCCAA	CGGCTGTACT GTGGAGGGCC CATGTATAAC AGCAAGGGCC
19		71	GCACGCGCGG	CAATACGGTC	ACTCACCCAA	CGGCTGTACT GTGGAGGGCC CATGTATAAC AGCAAGGGCC
=====						
20	GIV	71	GCCAGGAAAG	TGATCTCCTC	CCTCACGGAG	CGGCTTTACT GCGGGGGGCC TATGTTCAAC AGCAAGGGGG
21		71	GCCAGGAAAG	TGATCTCCTC	CCTCACGGAG	CGGCTTTACT GCGGGGGGCC TATGTTCAAT AGCAAGGGGG
22		71	GCCAGGAAAG	TGATCTCCTC	CCTCACGGAA	CGGCTTTACT GCGGGGGGCC TATGTTCAAC AGCAAGGGGG

SUBSTITUTE SHEET

4/21

Fig. 2c

NS5 REGION - (3/5)

SEQUENCE	ID NUMBER	GENOTYPE	
1	141	GI	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
2	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
3	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
4	141		AAAACCTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
5	141		AAAACCTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
6	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGGTACT GACAACTAGC TGTGGTAACA CCTTCACCTTG
7	141	GII	AGAACTGCGG CTATCGCCGG TGCCGCGCGA GCGGCGGTGCT GACGACTAGC TGCGGTAATA CCTTCACATG
8	141		AGAACTGCGG CTATCGCCGA TGCCGCGCGA GCGGCGGTGCT GACGACTAGC TGCGGTAATA CCTTCACATG
9	141		AGAACTGCGG TTATCGCCGG TGCCGCGCGA GCGGCGGTACT GACGACCAGC TGCGGTAATA CCTTTACATG
10	141		AGAACTGCGG TTATCGCCGG TGCCGCGCGA GCGGCGGTGCT GACGACTAGC TGCGGTAATA CCTTCACATG
11	141		AGAACTGCGG CTATCGCCGG TGCCGCGCGA GCGGCGGTGCT GACGACTAGC TGCGGTAACA CCTTCACATG
12	141		AGAACTGCGG CTATCGCCGG TGCCGCGCGA GCGGCGGTGCT GACGACTAGC TGCGGTAATA CCTTCACATG
13	141	GIII	AGAACTGCGG GTACAGGCGT TGCCGCGCGA GCGGCGGTGCT CACCACCTAGC ATGGGGAACA CCATCACATG
14	141		AATCCTGCGG GTACAGGCGT TGCCGCGCGA GCGGCGGTGCT CACCACCTAGC ATGGGGAACA CACTCACGTG
15	141		AATCCTGCGG GTACAGGCGT TGCCGCGCGA GCGGCGGTGCT CACCACCTAGC ATGGGGAACA CGCTCACGTG
16	141		AATCCTGCGG GTACAGGCGT TGCCGCGCGA GCGGCGGTGCT CACCACCTAGC ATGGGTAACA CACTCACGTG
17	141		AATCCTGCGG TTACAGGCGT TGCCGCGCGA GCGGCGGTCTT CACCACCTAGC ATGGGGAACA CCATGACATG
18	141	GV	AACAATGTGG TTATCGTAGA TGCCGCGCGA GCGGCGGTCTT CACCACCTAGT ATGGGGAACA CCATGACGTG
19	141		AACAATGTGG TTATCGTAGA TGCCGCGCGA GCGGCGGTCTT CACCACCTAGT ATGGGGAACA CCATGACGTG
20	141	GIV	CCCAGTGTGG TTATCGCCGT TGCCGTGCTA GTGGAGTCTT GCCTACCAGC TTCGGGAACA CAATCCTTG
21	141		CCCAGTGTGG TTATCGCCGT TGCCGTGCTA GTGGAGTCTT GCCTACCAGC TTCGGGAACA CAATCCTTG
22	141		CCCAGTGTGG TTATCGCCGT TGCCGTGCTA GTGGAGTCTT GCCTACCAGC TTCGGGAACA CAATCCTTG

SUBSTITUTE SHEET

5/21

Fig. 2d

NS5 REGION - (4/5)

SEQUENCE			ID NUMBER		GENOTYPE		
1	211	GI	CTACATCAAG	GCCCGGGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
2	211		CTACATCAAG	GCCCGGGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
3	211		CTACATCAAG	GCCCGGGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
4	211		CTACATTAAG	GCCCGGGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
5	211		TTACATCAAG	GCCCAAGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
6	211		TTACATCAAG	GCCCGGGCAG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
7	211	GII	CTACCTGAAG	GCCACAGCGG	CCTGTCGAGC	TGCAAGGCTC	CAGGACTGCA
8	211		TTACTTGAAG	GCCACTGCGG	CCTGTCGAGC	TGCAAGGCTC	CAGGACTGCA
9	211		TTACTTGAAG	GCCCTGCGG	CCTGTCGAGC	CGCAGGGGCTC	CAGGACTGCA
10	211		TTACTTGAAG	GCCCTGCGG	CCTGTCGAGC	TGCAAGGCTC	CAGGACTGCA
11	211		TTACTTGAAG	GCCCTGCGG	CCTGTCGAGC	TGCAAGGCTC	CAGGACTGCA
12	211		TTACTTGAAG	GCCAGTGGCG	CCTGTCGAGC	TGCAAGGCTC	CAGGACTGCA
13	211	GIII	CTATGTAAAG	GCCCTAGCGG	CTTGCAAGGC	TGCAGGGGATA	GTTGCACCCCT
14	211		CTACGTAAAG	GCCAGGGCGG	CCTGTAAACG	CGCGGGGATT	GTTGCTCCCA
15	211		CTACGTAAAG	GCCAGGGCGG	CCTGTAAACG	CGCGGGGATT	GTTGCTCCCA
16	211		CTACGTAAAG	GCTAAAGCGG	CATGTAAACG	CGCGGGGATT	GTTGCTCCCA
17	211		CTACATCAAG	GCCCTTGCAG	CTTGCAAGGC	TGCAGGGGATA	GTTGCACCCCT
18	211	GV	CTACATTAAG	GCTTTAGCCT	CCTGTAGAGC	CGCAAGGCTC	CAGGACTGCA
19	211		CTACATCAAG	GCTTCAGCCG	CCTGTAGAGC	TGCAAGGCTC	CAGGACTGCA
20	211	GIV	TTACATCAAG	GCTAGAGCGG	CTTGCAAGGC	CGCAGGGGCTC	CAGGACTGCA
21	211		TTACATCAAG	GCTAGAGCGG	CTTGCAAGGC	CGCAGGGGCTC	CAGGACTGCA
22	211		TTACATCAAG	GCTAGAGCGG	CTTGCAAGGC	CGCAGGGGCTC	CAGGACTGCA

SUBSTITUTE SHEET

Fig. 2e

NS5 REGION - (5/5)

6/21

SEQUENCE			ID NUMBER		GENOTYPE
1	281	GI	GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG GTCCAGGAGG ACGCGCGGAG CCTGAGAGCC
2	281		GACTTAGTCG	TTATCTGTGA	AAGTGCAGGG GTCCAGGAGG ACGCGCGGAG CCTGAGAGCC
3	281		GACTTAGTCG	TTATCTGTGA	GAGTGCAGGG GTCCAGGAGG ACGCGCGGAG CCTGAGAGCC
4	281		GACTTAGTCG	TTATCTGTGA	GAGTGCAGGG GTCCAGGAGG ACGCGCGGAG CCTGAGAGCC
5	281		GACTTAGTCG	TTATCTGTGA	AAGTGCAGGG GTCCAGGAGG ATGCAGCGAA CCTGAGAGCC
6	281		GACTTAGTCG	TTATCTGTGA	AAGTGCAGGG GTCCAGGAGG ACGCGCGGAG CCTGAGAGCC
7	281	GII	GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG AACCAAGAGG ACGCGCGAAG CCTACGAGCC
8	281		GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG ACCCAGGAGG ATGCGCGGAG CCTACGAGTC
9	281		GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG ACCCAGGAGG ACGCGCGGAA CCTACGAGTC
10	281		GACTTAGTCG	TTATCTGTGA	GAGCGCGGGG ACCCAGGAGG ACGCGCGGAG CCTACGAGTC
11	281		GACTTAGTCG	TTATCTGTGA	GAGCGCGGGG ACCCAGGAGG ACGCGCGGAG CCTACGAGTC
12	281		GACTTAGTCG	TTATCTGTGA	GAGCGCGGGG ACCCAGGAGG ACGCGCGGAG CCTACGAGTC
13	281	GIII	GACTTAGTCG	TCATCTCAGA	AAGCCAGGGG ACTGAGGAGG ACGAGCGGAA CCTGAGAGCT
14	281		GACTTAGTCG	TCATCTCAGA	GAGTCAAGGG GCTGAGGAGG ACGAGCAGAA CCTGAGAGTC
15	281		GACTTAGTCG	TCATCTCAGA	GAGTCAAGGG GCTGAGGAGG ACGAGCAGAA CCTGAGAGTC
16	281		GACTTAGTCG	TCATCTCAGA	GAGTCAAGGG GCTGAGGAGG ATGAGCGGAA CCTGAGAGCT
17	281		GACTTAGTCG	TCATCTCAGA	GAGCGAAGGT AACGAGGAGG ACGAGCGGAA CCTGAGAGCT
18	281	GV	GACTTAGTCG	CCATTGCGGA	GAGCCAGGGG ACGCAGGAGG ATAAAGCAG CCTGAGAGCC
19	281		ACCTTAGTCG	CCATTGCGGA	GAGCCAGGGG ACGCAGGAGG ATAAAGCAG CCTGAGAGTC
20	281	GIV	GACTTAGTCG	TGGTGGCTGA	GAGTGATGGC GTCGACGAGG ATAGAGCAGC CCTGAGAGCC
21	281		GACTTAGTCG	TGGTGGCTGA	GAGTGATGGC GTCGACGAGG ATAGAGCAGC CCTGAGAGCC
22	281		GACTTAGTCG	TGGTGGCTGA	GAGTGATGGC GTCGACGAGG ATAGAGCAGC CCTGAGAGCC

340 TOTAL

SUBSTITUTE SHEET

Fig. 3

ENVELOPE REGION

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
23	1	GI	GACGGCGTTG GTAATGGCTC AGCTGCTCCG GATCCACAA GCCATCTTGG ACATGATCGC
24	1		GACGGCGTTG GTGGTAGCTC AGGTACTCCG GATCCACAA GCCATCATGG ACATGATCGC
25	1		AACGGCGCTG GTAGTAGCTC AGCTGCTCAG GTCCCGCAA GCCATCGTGG ACATGATCGC
26	1	GII	GACAGCCCTA GTGGTATCGC AGTTACTCCG GATCCACAA GCCGTCATGG ATATGGTGGC
27	1		AGCAGCCCTA GTGGTGTCCG AGTTACTCCG GATCCACAA AGCATCGTGG ACATGGTGGC
28	1		GGCAGCCCTA GTGGTGTCCG AGTTACTCCG GATCCCGCAA GCTGTCTGGG ACATGGTGGC
29	1	GIV	TGTGGGTATG GTGGTGGCGC AGTCTCTGGG TTGCCCCCAG ACCTTGTTCG ACATAATAGC
30	1		TGTGGGTATG GTGGTAGCAC AGTCTCTGGG TTGCCCCCAG ACCTTGTTCG ACATAATAGC
31	1		TGTGGGTATG GTGGTGGCGC AAGTCTCTGG TTGCCCCCAG ACCTTGTTCG ACGTGCTAGC
32	1	GIII	TACCACTATG CTCTGGCAT ACTTGGTGGG CATCCCGGAG GTCATCTCTGG ACATTATCAC
23	61	GI	TGGTGCTCAC TGGGGAGTCC TGGCGGGCAT AGCGTATTTC
24	61		TGGAGCCAC TGGGGAGTCC TGGCGGGCAT AGCGTATTTC
25	61		TGGTGCCAC TGGGGAGTCC TAGCGGGCAT AGCGTATTTC
26	61	GII	GGGGCCAC TGGGGAGTCC TGGCGGGCCT TGCCTACTAT
27	61		GGGGCCAC TGGGGAGTCC TGGCGGGCCT TGCCTACTAT
28	61		GGGGCCAC TGGGGAATCC TAGCGGGTCT TGCCTACTAT
29	61	GIV	CGGGCCCAT TGGGGCATCT TGGCGGGCCT TGCCTATTAC
30	61		CGGGCCCAT TGGGGCATCT TGGCAGGCCT AGCCTATTAC
31	61		CGGGCCCAT TGGGGCATCT TGGCGGGCCT TGCCTATTAC
32	61	GIII	GGGAGGACAC TGGGGCGTGA TGTGGCCT TGCCTATTTC

100 Total

SUBSTITUTE SHEET

8/21

Fig. 4a

5'UT Region

SEQUENCE			5'UT Region	
ID NUMBER	GENOTYPE			
33	GI	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
34		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
35		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
36		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
37		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
38		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
39	GII	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
40		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
41		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
42		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
43		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
44		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
45		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
46	GIII	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
47		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
48	GIV	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
49		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
50	GV	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	
51		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC CGGAGAGGCC ATAGTGGTCT	

SUBSTITUTE SHEET

9/21

Fig. 4b

5'UT Region (2/5)

SEQUENCE			=====		
ID NUMBER	GENOTYPE		=====		
33	GI	61	GC	GA	ACCGG
34		61	GC	GA	ACCGG
35		61	GC	GA	ACCGG
36		61	GC	GA	ACCGG
37		61	GC	GA	ACCGG
38		61	GC	GA	ACCGG
39	GII	61	GC	GA	ACCGG
40		61	GC	GA	ACCGG
41		61	GC	GA	ACCGG
42		61	GC	GA	ACCGG
43		61	GC	GA	ACCGG
44		61	GC	GA	ACCGG
45		61	GC	GA	ACCGG
46	GIII	61	GC	GA	ACCGG
47		61	GC	GA	ACCGG
48	GIV	61	GC	GA	ACCGG
49		61	GC	GA	ACCGG
50	GV	61	GC	GA	ACCGG
51		61	GC	GA	ACCGG

SUBSTITUTE SHEET

Fig. 4c

5'UT Region (3/5)

10/21

SEQUENCE			=====		
ID NUMBER	GENOTYPE		=====		
33	121	GI	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
34	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
35	121		GCTCAATGCC	TGGAGATTG	GGCACGCCCC CGCAAGATCA CTAGCCGAGT AGTGTGGGT
36	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
37	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
38	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
=====					
39	121	GII	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
40	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
41	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
42	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
43	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
44	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
45	121		GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
=====					
46	121	GIII	ACTCTATGCC	CGGCCATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGCGTTGGT
47	121		ACTCTATGCC	CAGCCATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGCGTTGGT
=====					
48	121	GIV	GCTCAATACC	CAGAAATTG	GGCGTGCCCC CGCGAGATCA CTAGCCGAGT AGTGTGGGT
49	121		GCTCAATACC	CAGAAATTG	GGCGTGCCCC CGCGAGATCA CTAGCCGAGT AGTGTGGGT
=====					
50	121	GV	GCTCAATGCC	CGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
51	121		GCTCAATGCC	CGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
=====					

SUBSTITUTE SHEET

11/21

Fig. 4d

ENVELOPE REGION (4/5)

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
33	181	GI	CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
34	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
35	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
36	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
37	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
38	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
39	181	GII	CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
40	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
41	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
42	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
43	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
44	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
45	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
46	181	GIII	TGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
47	181		TGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
48	181	GIV	CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT
49	181		CGCGAAAGGC CTTGTGGTAC TGCCTGATAG GGTGCTTGCG AGTGCCCCCGG GAGGTCCTCGT

SUBSTITUTE SHEET

12/2/

Fig. 4e

5'UT Region (5/5)

SEQUENCE	ID NUMBER	GENOTYPE
=====		
33	GI	241 AGACCGTGCA CC
34		241 AGACCGTGCA CC
35		241 AGACCGTGCA CC
36		241 AGACCGTGCA CC
37		241 AGACCGTGCA CC
38		241 AGACCGTGCA CC
=====		
39	GII	241 AGACCGTGCA CC
40		241 AGACCGTGCA TC
41		241 AGACCGTGCA CC
42		241 AGACCGTGCA CC
43		241 AGACCGTGCA CC
44		241 AGACCGTGCA CC
45		241 AGACCGTGCA CC
=====		
46	GIII	241 AGACCGTGCA TC
47		241 AGACCGTGCA TC
=====		
48	GIV	241 AGACCGTGCA AC
49		241 AGACCGTGCA AC
=====		
252 Total		

SUBSTITUTE SHEET

13/21

Fig. 5a

CORE REGION

SEQUENCE			CORE REGION	
ID NUMBER	GENOTYPE			
52	GI	1	ATGAGCACGA ATCCTAAACC TCAAAAAAAA AACAAACGTA ACACCAACCG TCGCCCCACAG	
53		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
54		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
55		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
56		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
57		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
58	GII	1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
59		1	ATGAGCACAA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
60		1	ATGAGCACAA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG	
61		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
62		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
63		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
64		1	ATGAGCACGA ATCCTAAACC TCAAAAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG	
65	GIII	1	ATGAGCACAA ATCCTAAACC TCAAAAGAAA ACCAAAGAA ACACCTAACCG CCGCCCCACAG	
66		1	ATGAGCACAA ATCGTCAACC TCAAAAGAAA ACCAAAGAA ACACCTAACCG CCGCCCCACAG	

SUBSTITUTE SHEET

14/21

Fig. 5b

CORE REGION (2/9)

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
52	GI	61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
53		61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
54		61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
55		61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
56		61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
57		61	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
58	GII	61	GACGTCAAGT TCCCGGGGCG TGGCCAGGTC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
59		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
60		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
61		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
62		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
63		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
64		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGTGGAG TTTACTTGT GCGCGGCAGG
65	GIII	61	GACGTCAAGT TCCCGGGGCG TGGCCAGATC GTTGGCGGAG TATACTTGT GCGCGGCAGG
66		61	GACGTCAAGT TCCCGGGGCG TGGTCAGATC GTTGGCGGAG TATACTTGT GCGCGGCAGG

SUBSTITUTE SHEET

Fig. 5c

CORE REGION (3/9)

15721

SEQUENCE	ID NUMBER	GENOTYPE	
52	121	G1	GGCCCTAGAT TGGGTGTGCG CGCGACGAGA AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
53	121		GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
54	121		GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
55	121		GGCCCTAGAT TGGGTGTGCG CACGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
56	121		GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
57	121		GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGT
58	121	G11	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
59	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
60	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
61	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
62	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
63	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
64	121		GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
65	121	G111	GGCCCCAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AACGATCCCA GCCACGCCGA
66	121		GGCCCCAGGT TGGGTGTGCG CGCGACGAGG AAGACTTCCG AACGATCCCA GCCACGTGGG

SUBSTITUTE SHEET

Fig. 5d

CORE REGION (479)

16121

SEQUENCE	ID NUMBER	GENOTYPE	
52	181	G1	AGACGTCAGC CTATCCCCAA GGCTCGTCGG CCGAGGGCA GGACCTGGGC TCAGCCCGGG
53	181		AGACGTCAGC CTATCCCCAA GGCGCTCGG CCGAGGGCA GGACCTGGGC TCAGCCCGGG
54	181		AGACGTCAGC CTATCCCCAA GGCGCTCGG CCGAGGGCA GGACCTGGGC TCAGCCCGGG
55	181		AGACGTCAGC CCATCCCCAA GGCTCGTCGA CCGAGGGCA GGACCTGGGC TCAGCCCGGG
56	181		AGACGTCAGC CTATCCCCAA GGACGTCGG CCGAGGGTA GGACCTGGGC TCAGCCCGGG
57	181		AGACGCCAGC CTATCCCCAA GGCGCTCGG CCGAGGGCA GGACCTGGGC TCAGCCCGGG
58	181	G11	AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGG b CA GGGCCTGGGC TCAGCCCGGG
59	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGCA GGGCCTGGGC TCAGCCCGGG
60	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGCA GGTCTTGGGC TCAGCCCGGG
61	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGTA GGGCCTGGGC TCAGCCCGGG
62	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGCA GGGCCTGGGC TCAGCCCGGG
63	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGCA GGGCCTGGGC TCAGCCCGGG
64	181		AGCGACAAC CTATCCCCAA GGCTGCCAG CCGAGGGCA GGGCCTGGGC TCAGCCCGGG
65	181	G111	AGCGTCAGC CCATCCCTAA AGATCTCGC ACCGCTGGCA AGTCCTGGGG AAGCCAGGA
66	181		AGCGCCAGC CCATCCCTAA AGATCGGCG ACCACTGGCA AGTCCTGGGG GAAGCCAGGA

SUBSTITUTE SHEET

17/21

Fig. 5e

CORE REGION (5'9)

SEQUENCE			=====					
ID NUMBER	GENOTYPE		=====					
=====								
52	GI	241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGC	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
53		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
54		241	TACCCCTTGGC	CCCTCTATGG	TAATGAGGGT	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
55		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGC	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
56		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
57		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	TGCGGGTGGG	CGGGATGGCT	CCTGTCTCCC
=====								
58	GII	241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCAACC
59		241	TACCCCTTGGC	CCCTCTATGG	CAACGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCAACC
60		241	TACCCCTTGGC	CCCTCTATGG	CAACGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCAACC
61		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCTCCC
62		241	TATCCTTGGC	CCCTCTATGG	CAATGAGGGT	CTGGGGTGGG	CAGGATGGCT	CCTGTCAACC
63		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCAACC
64		241	TACCCCTTGGC	CCCTCTATGG	CAATGAGGGT	ATGGGGTGGG	CAGGATGGCT	CCTGTCAACC
=====								
65	GIII	241	TATCCTTGGC	CCCTGTATGG	GAATGAGGGT	CTCGGCTGGG	CAGGATGGCT	CCTGTCTCCC
66		241	TACCCCTTGGC	CCCTGTATGG	GAATGAGGGT	CTCGGCTGGG	CAGGATGGCT	CCTGTCTCCC
=====								

SUBSTITUTE SHEET

18/2/

Fig. 5f

CORE REGION (6/9)

SEQUENCE			=====									
ID NUMBER	GENOTYPE		=====									
52	GI	301	CGTGGCTCTC	GGCCTAGCTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
53		301	CGTGGCTCTC	GGCCTAGTTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
54		301	CGTGGCTCTC	GGCCTAGTTG	GGGCTTACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
55		301	CGTGGCTCTC	GGCCTAGCTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
56		301	CGGCGTCTC	GGCCTAACTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
57		301	CGTGGCTCTC	GGCCTAGCTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
=====												
58	GII	301	CGTGGCTCTC	GGCCTAGTTG	GGGCCCCACG	GACCCCCCGC	GTAGGTCGCG	TAATTGGGGT	=====			
59		301	CGTGGCTCTC	GGCCTAGTTG	GGGCCCCACG	GACCCCCCGC	GTAGGTCGCG	TAATTGGGGT	=====			
60		301	CGGCGCTCCC	GGCCTAGTTG	GGGCCCCACG	GACCCCCCGC	GTAGGTCGCG	TAATTGGGGT	=====			
61		301	CGGCGCTCCC	GGCCTAGTTG	GGGCCCCACA	GACCCCCCGC	GTAGGTCGCG	TAATTGGGGT	=====			
62		301	CGGCGCTCTC	GGCCTAGCTG	GGGCGCTACC	GACCCCCCGC	GTAGGTCGCG	CAACTGGGGT	=====			
63		301	CGTGGTCTC	GGCCTAGTTG	GGGCCCCACG	GACCCCCCGC	GTAGGTCGCG	CAATTGGGGT	=====			
64		301	CGGCGCTCCC	GGCCTAGTTG	GGGCCCCAAA	GACCCCCCGC	GTAGGTCGCG	TAATTGGGGT	=====			
=====												
65	GIII	301	CGTGGCTCTC	GGCCTTCATG	GGGCCCCACT	GACCCCCCGC	ATAGATCAGG	CAACTGGGGT	=====			
66		301	CGGCGTCTC	GGCCTTCATG	GGGCCCCACT	GACCCCCCGC	ATAGATCAGG	CAACTGGGGT	=====			
=====												

SUBSTITUTE SHEET

Fig. 59

CORE REGION (7/9)

=====

SEQUENCE	ID NUMBER	GENOTYPE
52	361	G1
53	361	
54	361	
55	361	
56	361	
57	361	
58	361	G11
59	361	
60	361	
61	361	
62	361	
63	361	
64	361	
65	361	G111
66	361	

=====

19/21

SUBSTITUTE SHEET

20/21

Fig. 5h

CORE REGION (8/9)

SEQUENCE			GENOTYPE		SEQUENCE	
ID NUMBER						
52	421	GI	GGCGCCCTC	TTGGAGGCG	TGCCAGGGCC	CTGGCGCATG
53	421		GGCGCCCTC	TTGGAGGCG	TGCCAGGGCT	CGTCCGGGT
54	421		GGCGCCCTC	TTGGGGGCG	TGCCAGGGCC	CTGGCGCATG
55	421		GGCGCCCTC	TTGGAGGCG	TGCCAGAGCC	CGTCCGGGT
56	421		GGCGCCCTC	TTGGAGGCG	TGCCAGGGCC	CTGGCGCATG
57	421		GGCGCCCTC	TTGGAGGCG	TGCCAGGGCC	CTGGCGCATG
58	421	GI	GGCGCCCTC	TTAGGGGCG	TGCCAGGGCC	TTGGCGCATG
59	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
60	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
61	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
62	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
63	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
64	421		GGCGCCCTC	TAGGGGCG	TGCCAGGGCC	CTGGCGCATG
65	421	GI	GGCGCCCTC	TTGGAGGCG	TGCCAGAGCT	CTGGCGCATG
66	421		GGCGCCCTC	TTGGAGGCG	TGCCAGAGCC	CTGGCGCATG

SUBSTITUTE SHEET

2/2

Fig. 5i

CORE REGION (9/9)

SEQUENCE	ID	NUMBER	GENOTYPE	
52	GI	481	GGCGTGAAC	ATGCAACAGG
53		481	GGCGTGAAC	ATGCAACAGG
54		481	GGCGTGAAC	ATGCAACAGG
55		481	GGCGTGAAC	ATGCAACAGG
56		481	GGCGTGAAC	ATGCAACAGG
57		481	GGCGTGAAC	ATGCAACAGG
58	GII	481	GGCGTGAAC	ATGCAACAGG
59		481	GGCGTGAAC	ATGCAACAGG
60		481	GGCGTGAAC	ATGCAACAGG
61		481	GGCGTGAAC	ATGCAACAGG
62		481	GGCGTGAAC	ATGCAACAGG
63		481	GGCGTGAAC	ATGCAACAGG
64		481	GGCGTGAAC	ATGCAACAGG
65	GIII	481	GGCGTGAAC	ATGCAACAGG
66		481	GGCGTGAAC	ATGCAACAGG

549 Total